UNIVERSITY
CHILDREN'S HOSPITAL
ZURICH

Pigmentflecken und -mosaike

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Leitender Arzt
Zentrum Kinderhaut - Dermatologie

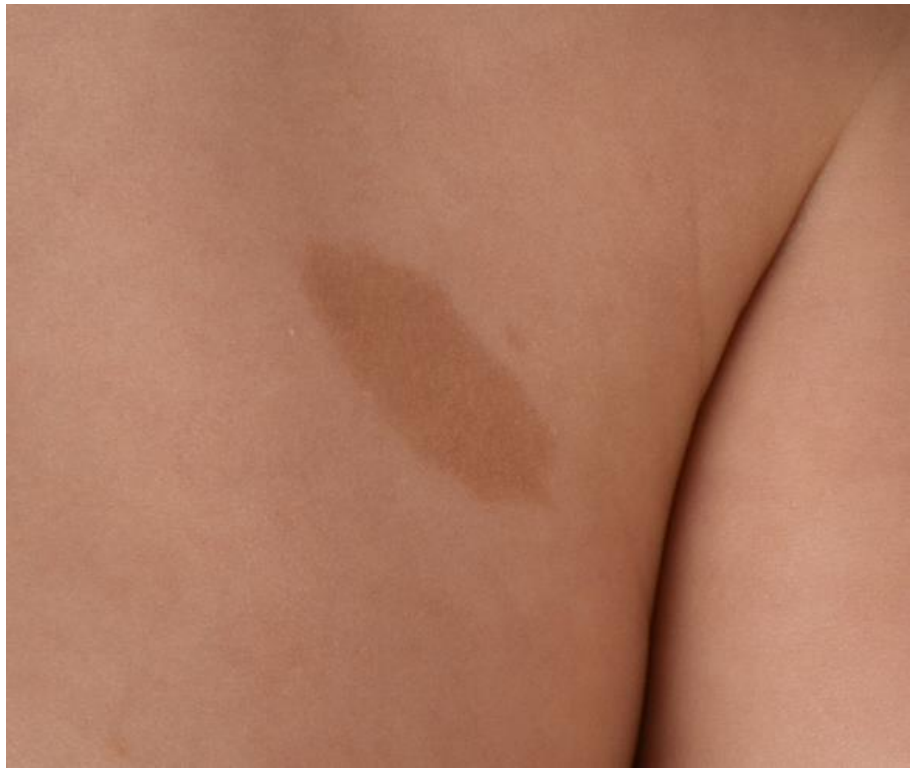
Normalbefund

Marker für Syndrom

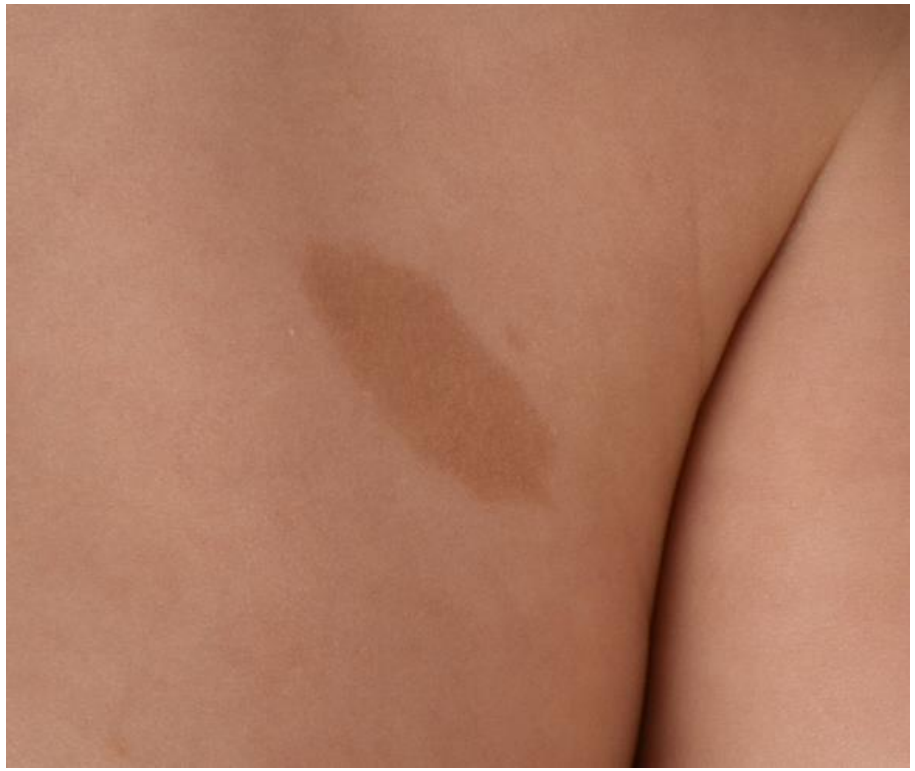
Café-au-lait Fleck (CALM)

Syndrome or grouping	Gene
Neurofibromatosis type 1	*NF1*
Mosaic NF1	*NF1*
Neurofibromatosis type 2, schwannomatosis, and multiple schwannoma	*NF2, SMARCB1, LTZR1*
Legius syndrome	*SPRED1*
Mosaic Legius syndrome	*SPRED1*
Constitutional mismatch repair deficiency syndrome (CMMRDS)[116]	*MSH2, MSH6, MLH1, PMS2*
PTEN hamartoma tumor syndrome	*PTEN*
RASopathies: (Noonan syndrome, Noonan syndrome with multiple lentigines, cardiofaciocutaneous syndrome, NF1, Legius yndrome, Noonan-like syndrome)	*HRAS, NRAS, KRAS, NF1, SPRED1, LZTR1, PTPN11, PPP1CB, BRAF, CBL, MAP2K1, MAP2K2, RAF1, RIT1, RASA2, SHOC2, SOS1, SOS2*
Chromosomal anomalies	N/A
McCune Albright syndrome	*GNAS*

Lalor L et al, Clin Dermatol 2020

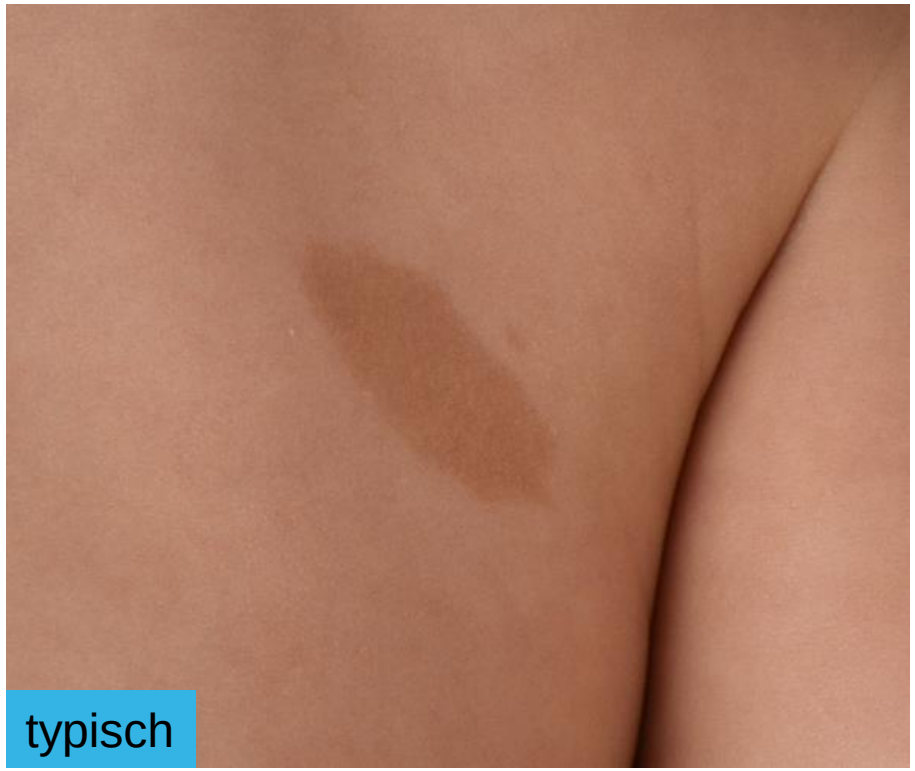


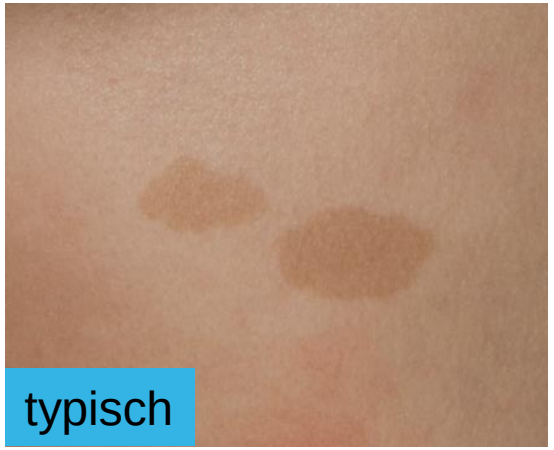
- Anzahl der CALM
- Morphologie
  «typisch» vs. «atypisch»
- Alter
- (Familien)Anamnese
  Ganzkörperstatus



Anzahl der CALM

1-3 CALM	→ 36% der gesunden Kinder
>3 CALM	→ 0.3% der Kinder → oft genetische Erkrankung

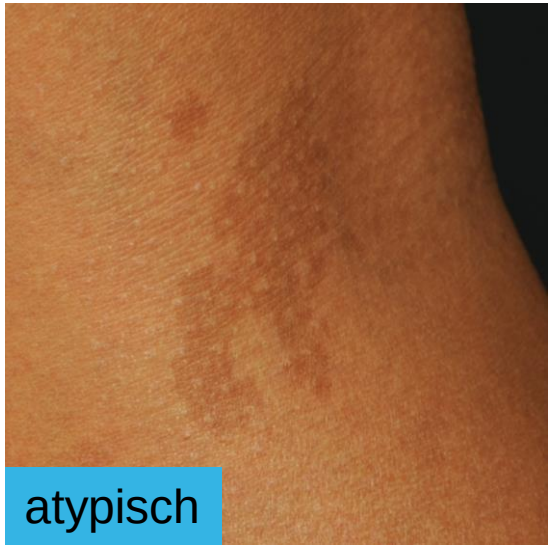




Scharf begrenzt, rundlich, homogen pigmentiert

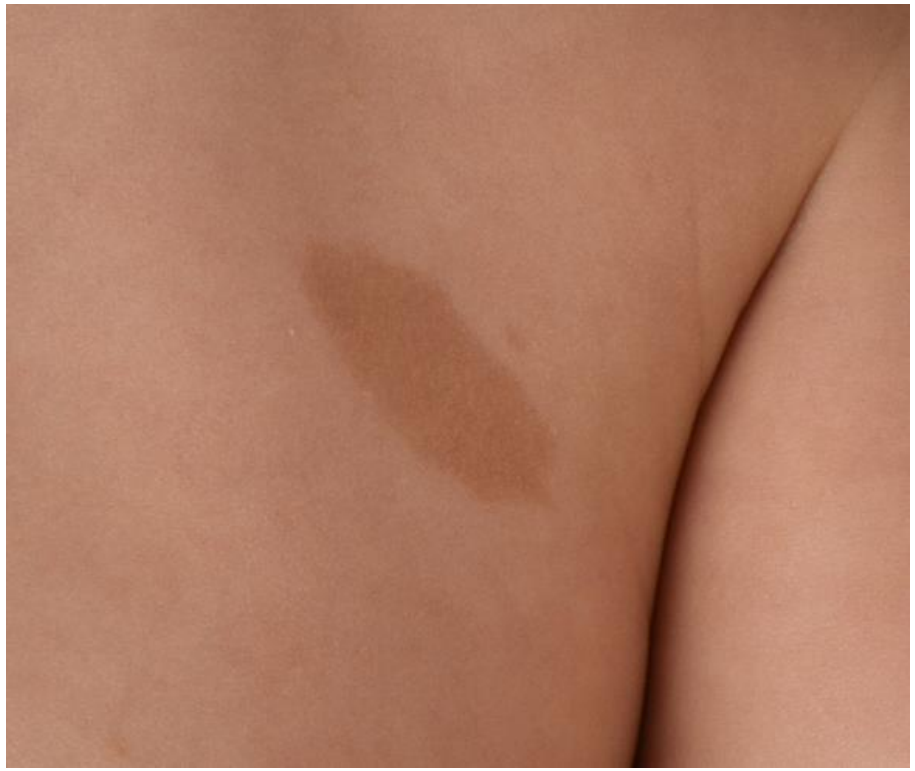
Multipel ➔
<u>starke</u> Assoziation mit NF1

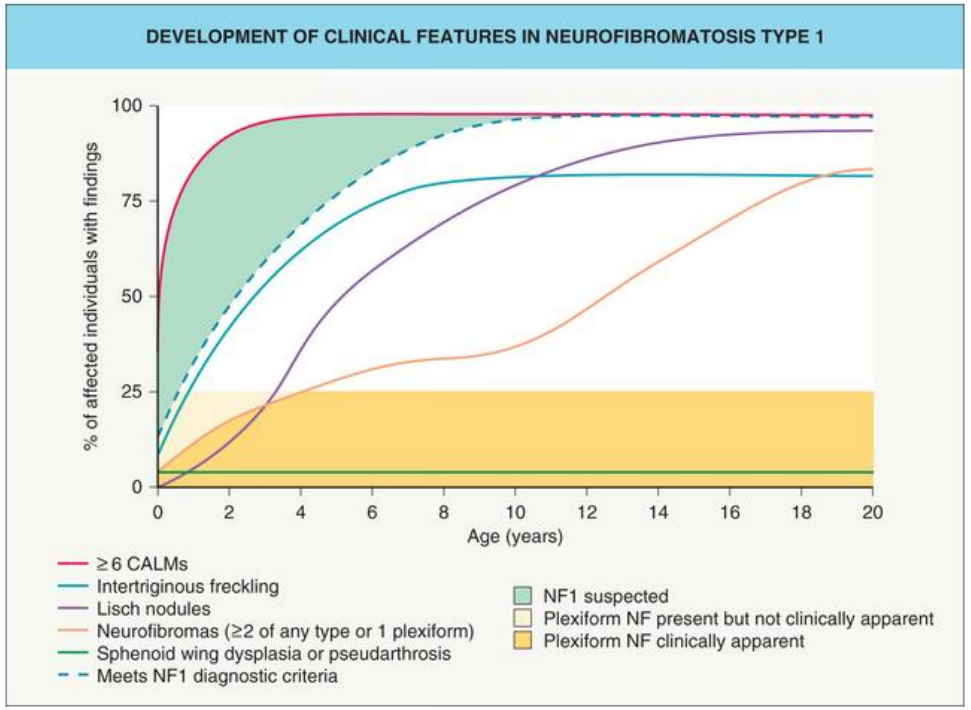
Morphologie
«typisch» vs. «atypisch»



Unregelmässig begrenzt, unterschiedlich pigmentiert

Multipel ➔
<u>schwache</u> Assoziation mit NF1, an andere Dinge denken!



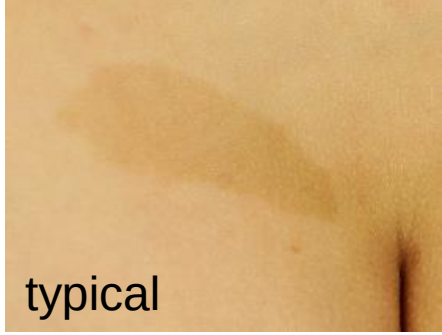


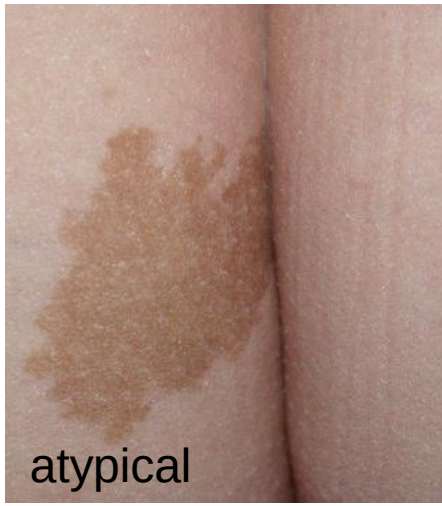
Alter

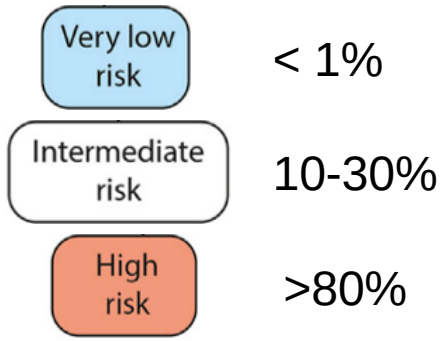
Klinische Diagnosekriterien für NF1 erfüllt:

- 54% mit 1 Jahr
- 95% mit 8 Jahren
- 100% mit 20 Jahren

Fig 2. Modified algorithm for detecting risk of neurofibromatosis 1 (*NF1*) among individuals with isolated café-au-lait macules (*CALMs*) based on clinical parameters.







Ben-Shachar et al, JAAD 2017

weitere Flecken

Sonstige kutane Veränderungen

Dysmorphiezeichen

Kopfumfang G, L

Thoraxfehlbildungen

Bewegungsapparat

Herzgeräusch

Haarauffälligkeiten

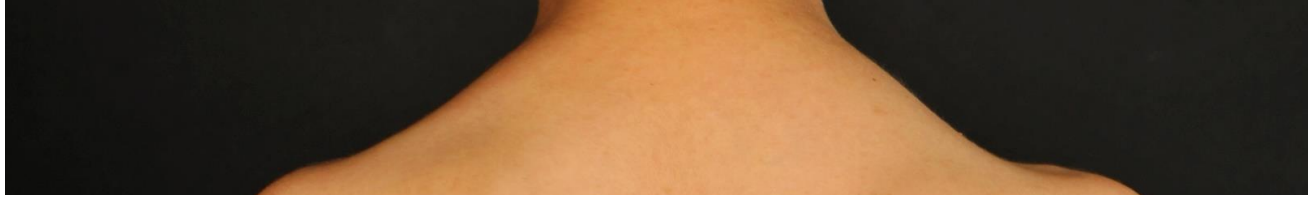


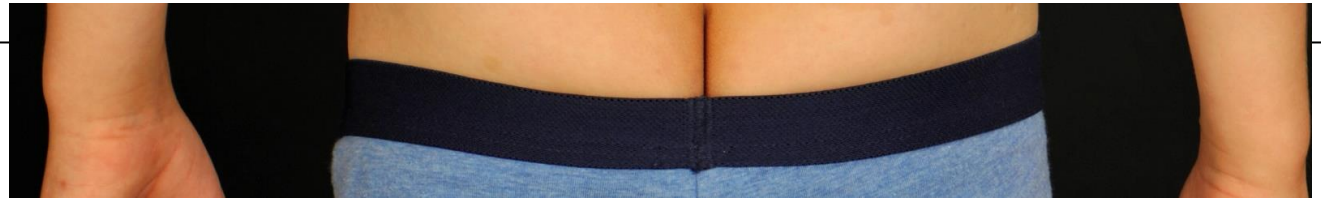
Table 1. Revised diagnostic criteria for neurofibromatosis type 1 (NF1).

A: The diagnostic criteria for NF1 are met in an individual who does not have a parent diagnosed with NF1 if two or more of the following are present:

- Six or more café-au-lait macules over 5 mm in greatest diameter in prepubertal individuals and over 15 mm in greatest diameter in postpubertal individuals[a] (Supplementary Fig. 6)
- Freckling in the axillary or inguinal region[a] (Supplementary Fig. 7)
- Two or more neurofibromas of any type *or* one plexiform neurofibroma (Supplementary Fig. 8a, b)
- Optic pathway glioma (Supplementary Fig. 9)
- Two or more iris Lisch nodules identified by slit lamp examination or two or more choroidal abnormalities (CAs)—defined as bright, patchy nodules imaged by optical coherence tomography (OCT)/near-infrared reflectance (NIR) imaging (Supplementary Fig. 10a, b)
- A distinctive osseous lesion such as sphenoid dysplasia,[b] anterolateral bowing of the tibia, or pseudarthrosis of a long bone (Supplementary Fig. 11)
- A heterozygous pathogenic *NF1* variant with a variant allele fraction of 50% in apparently normal tissue such as white blood cells

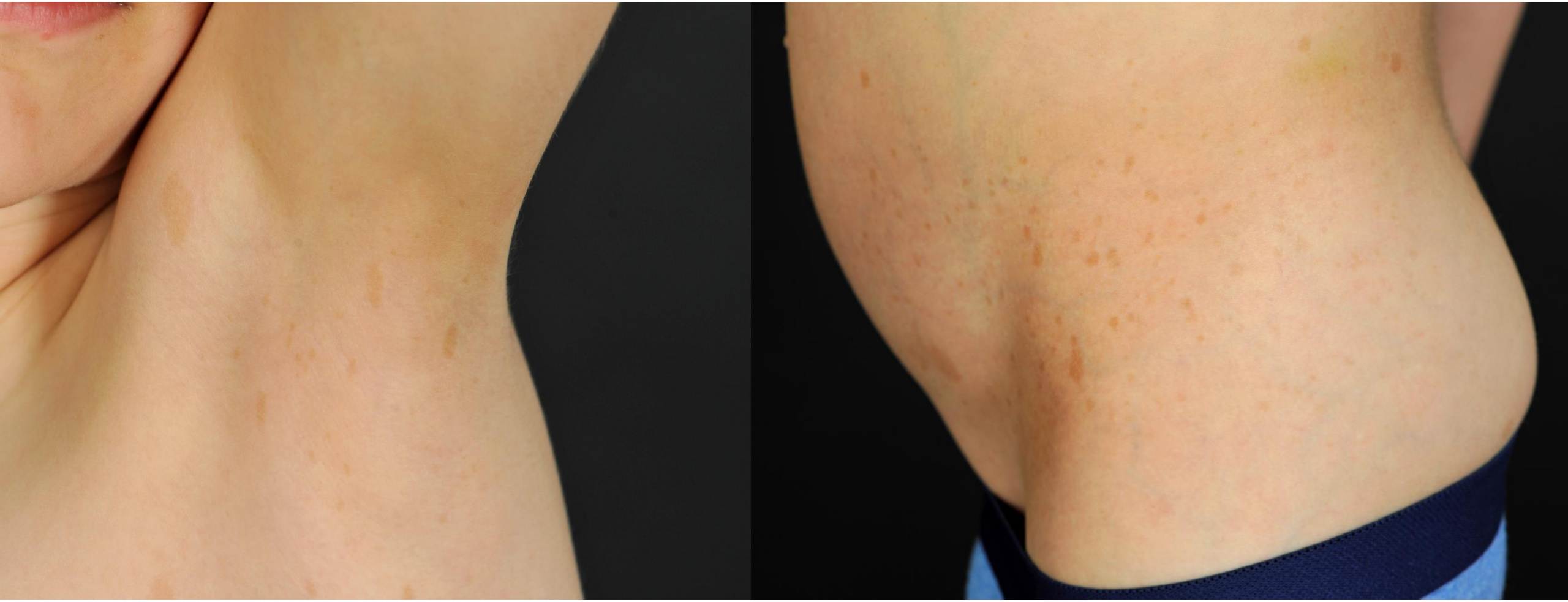
B: A child of a parent who meets the diagnostic criteria specified in A merits a diagnosis of NF1 if one or more of the criteria in A are present

[a]If only café-au-lait macules and freckling are present, the diagnosis is most likely NF1 but exceptionally the person might have another diagnosis such as Legius syndrome. At least one of the two pigmentary findings (café-au-lait macules or freckling) should be bilateral.
[b]Sphenoid wing dysplasia is not a separate criterion in case of an ipsilateral orbital plexiform neurofibroma.

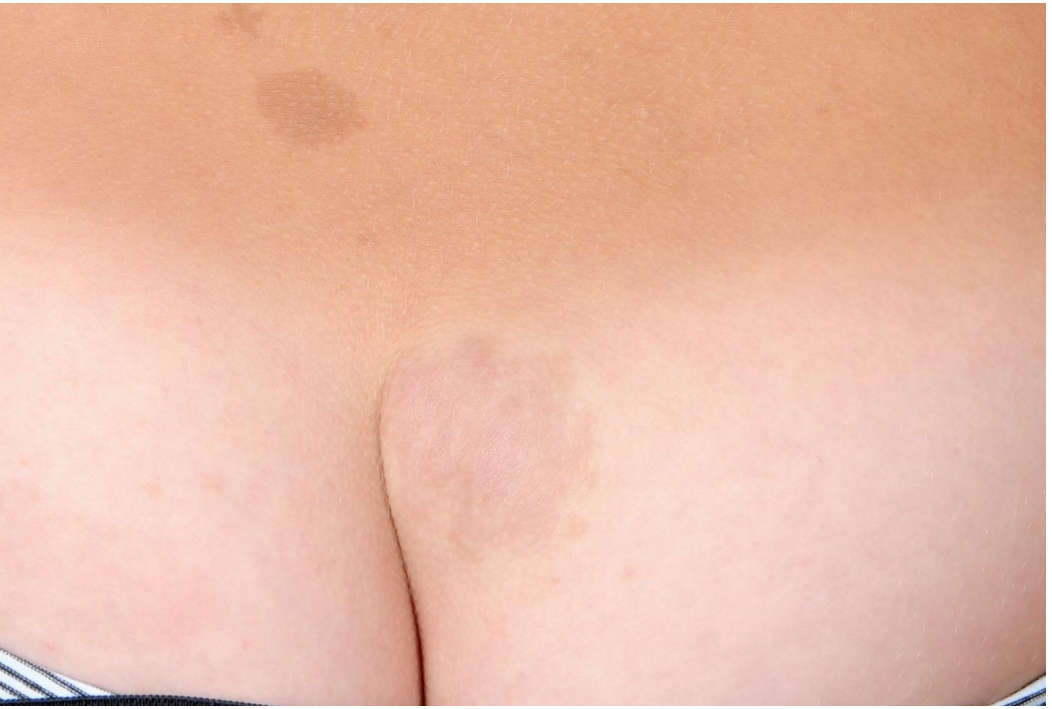


Neurofibromatose Typ 1

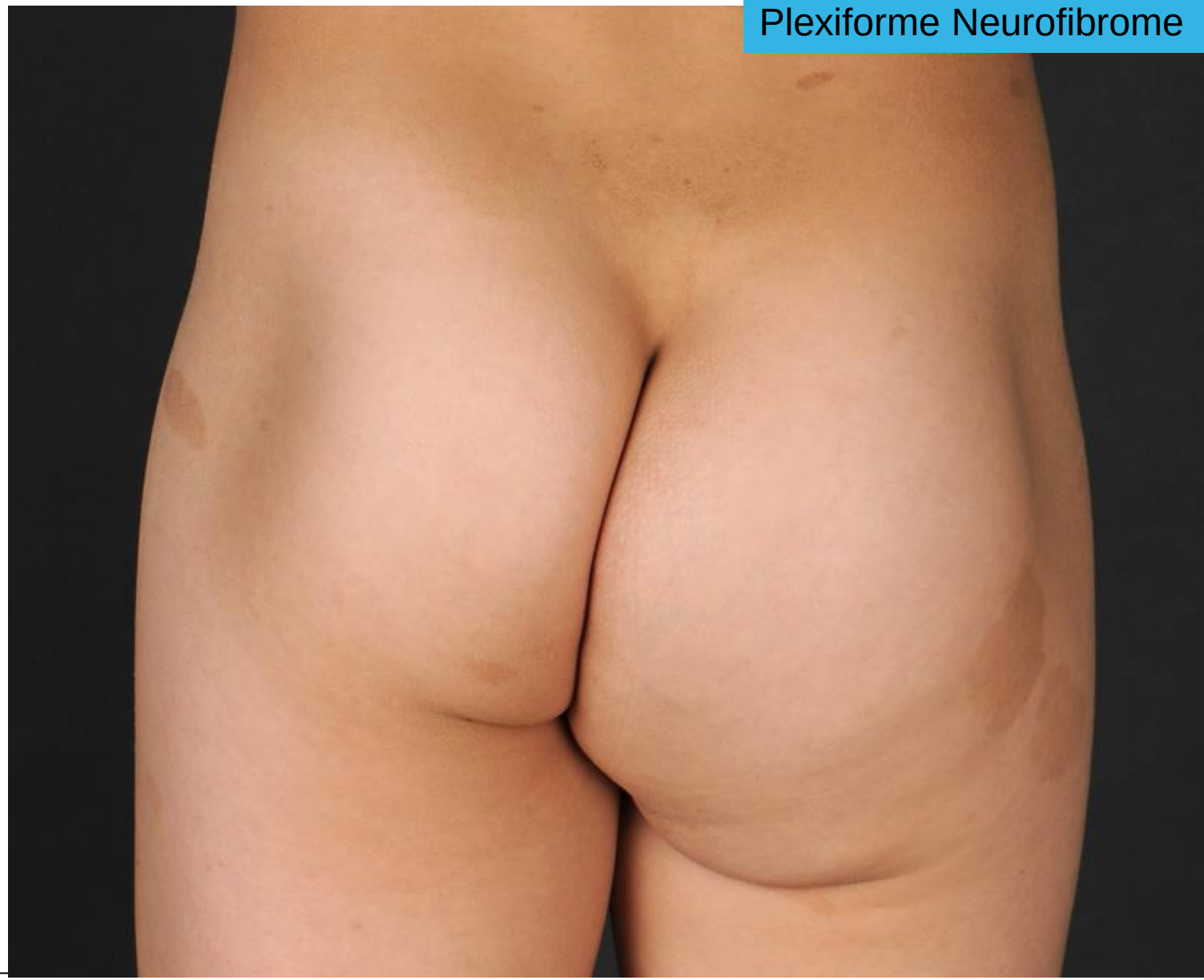
Diagnosekriterium
Intertriginöses Freckling



Neurofibromatose Typ 1

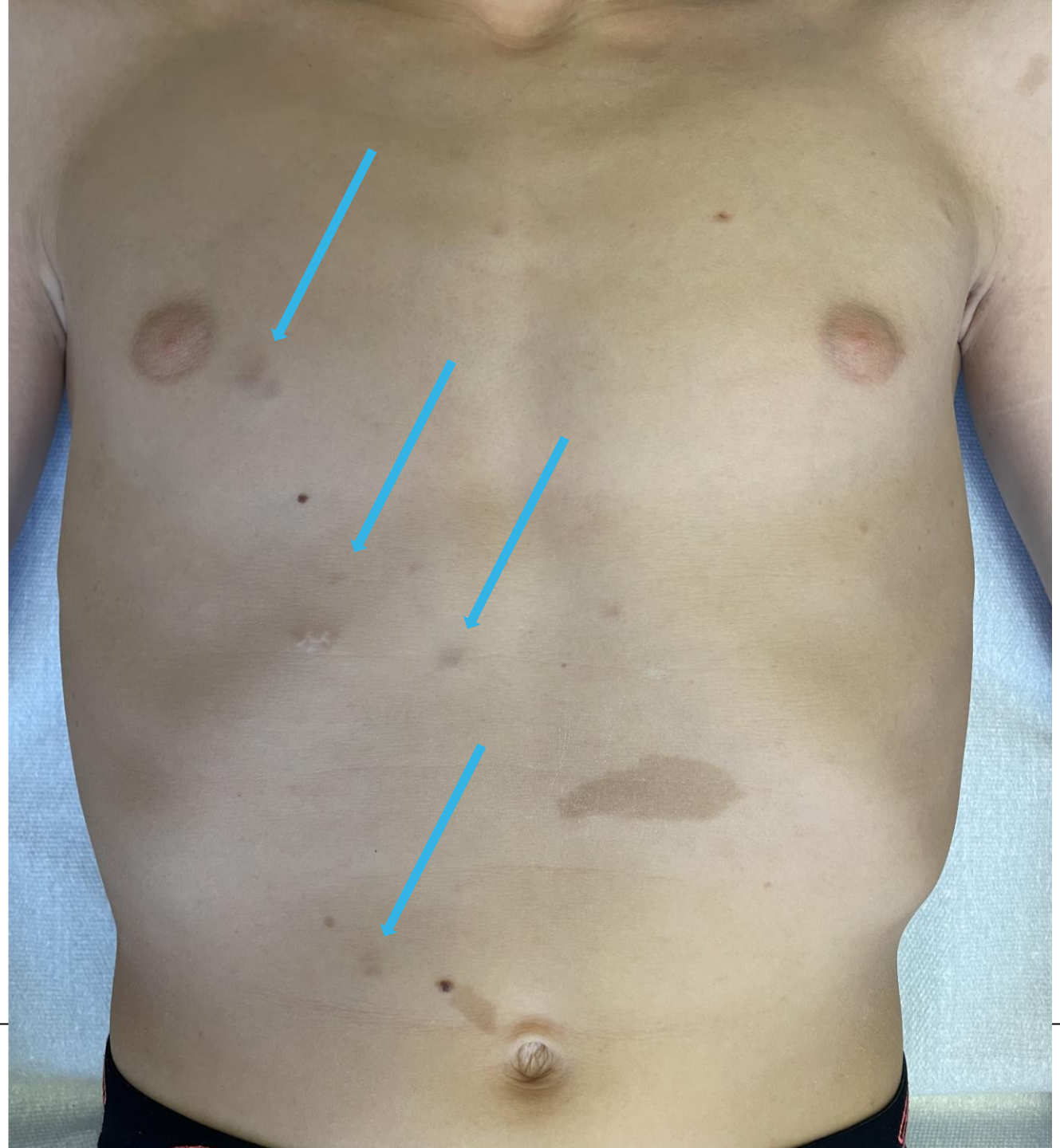


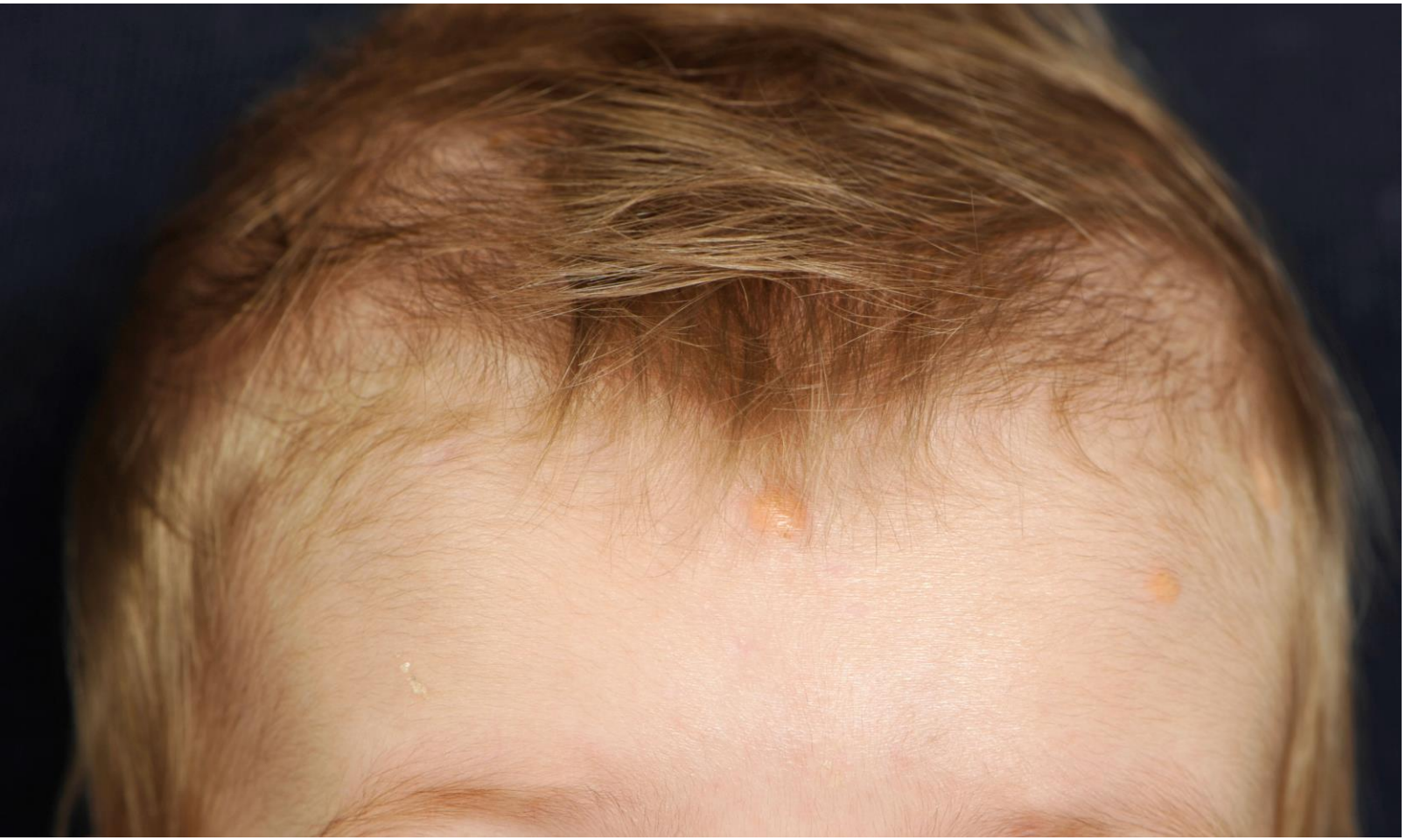
Diagnosekriterium
Plexiforme Neurofibrome



Neurofibromatose Typ 1

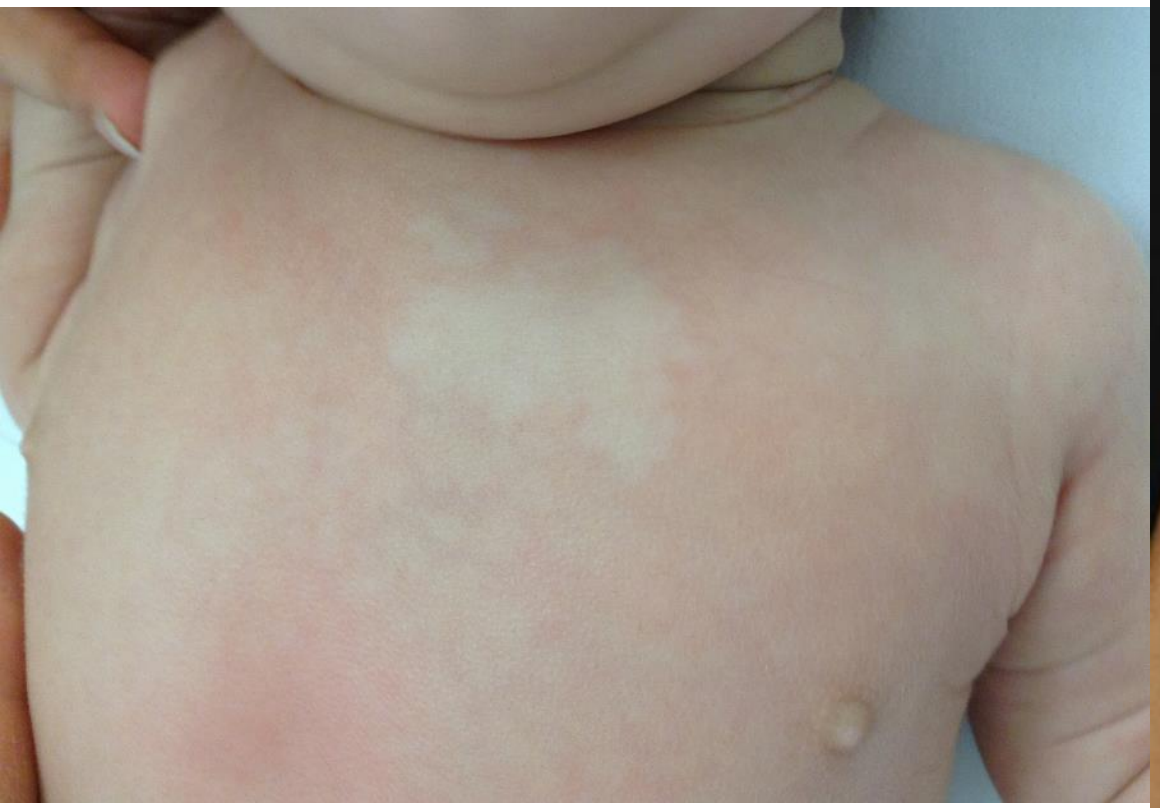
Diagnosekriterium
Erworbene Neurofibrome





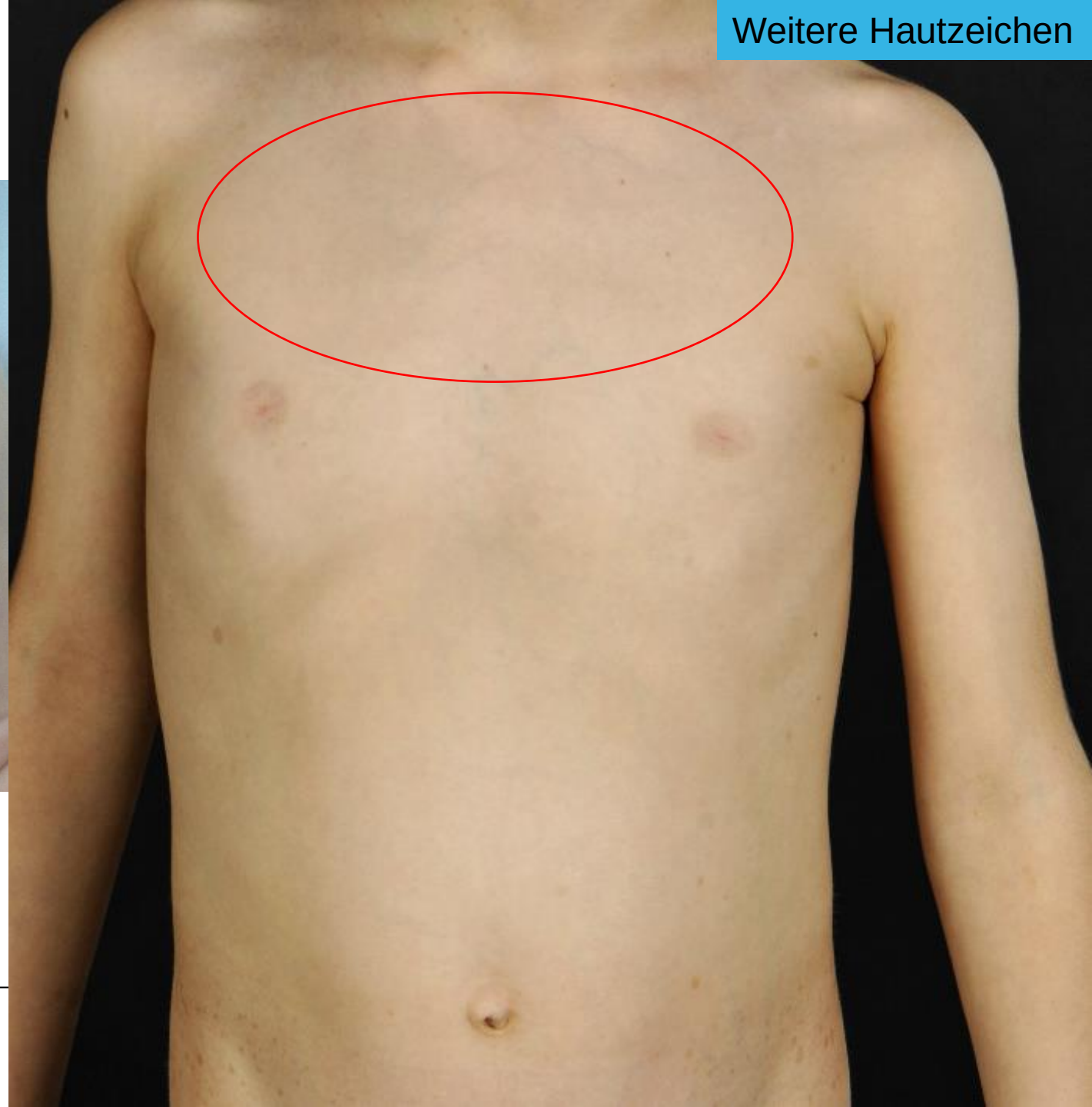
Juvenile Xanthogranulome 6-10%

Neurofibromatose Typ 1



Nävus anämicus 50%

Weitere Hautzeichen

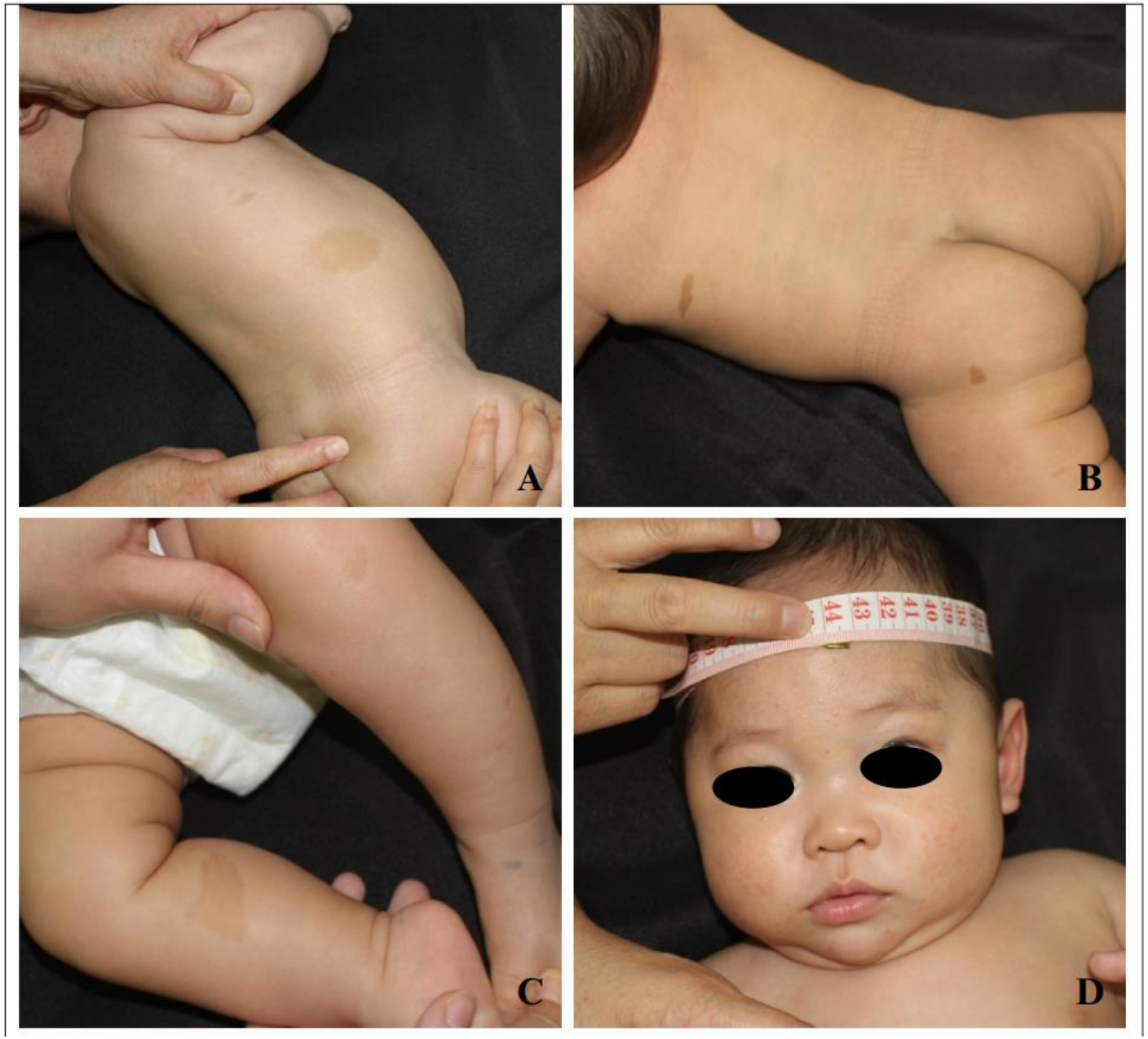


Legius syndrome	*SPRED1*
Constitutional mismatch repair deficiency syndrome (CMMRDS)[116]	*MSH2, MSH6, MLH1, PMS2*
PTEN hamartoma tumor syndrome	*PTEN*
RASopathies: (Noonan syndrome, Noonan syndrome with multiple lentigines, cardiofaciocutaneous syndrome, NF1, Legius yndrome, Noonan-like syndrome)	*HRAS, NRAS, KRAS, NF1, SPRED1, LZTR1, PTPN11, PPP1CB, BRAF, CBL, MAP2K1, MAP2K2, RAF1, RIT1, RASA2, SHOC2, SOS1, SOS2*
Chromosomal anomalies	N/A
McCune Albright syndrome	*GNAS*

Lalor L et al, Clin Dermatol 2020

Legius Syndrom

SPRED1



Chen L et al, EJD 2023

Mehrere typische/atypische CALM

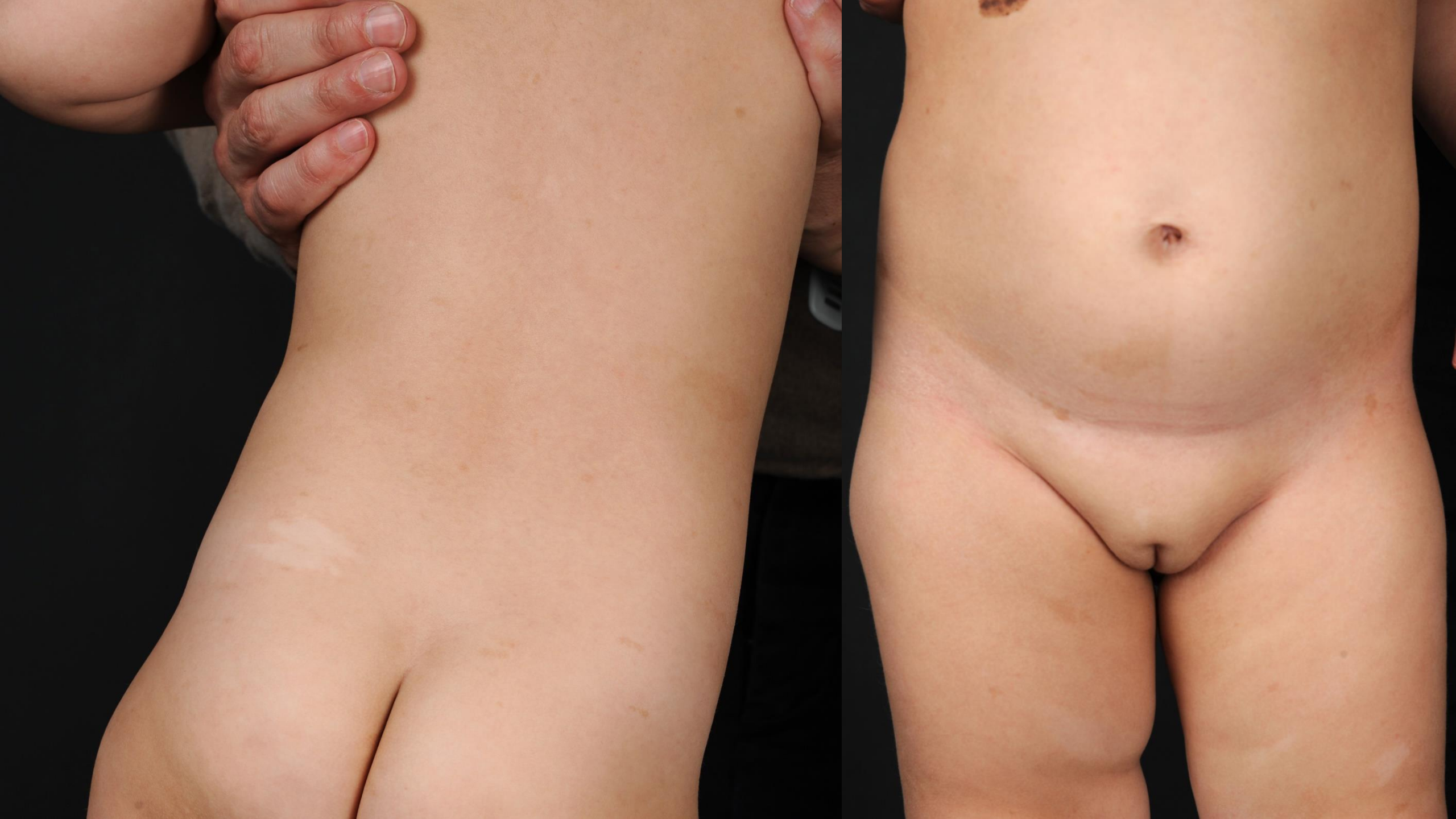
+

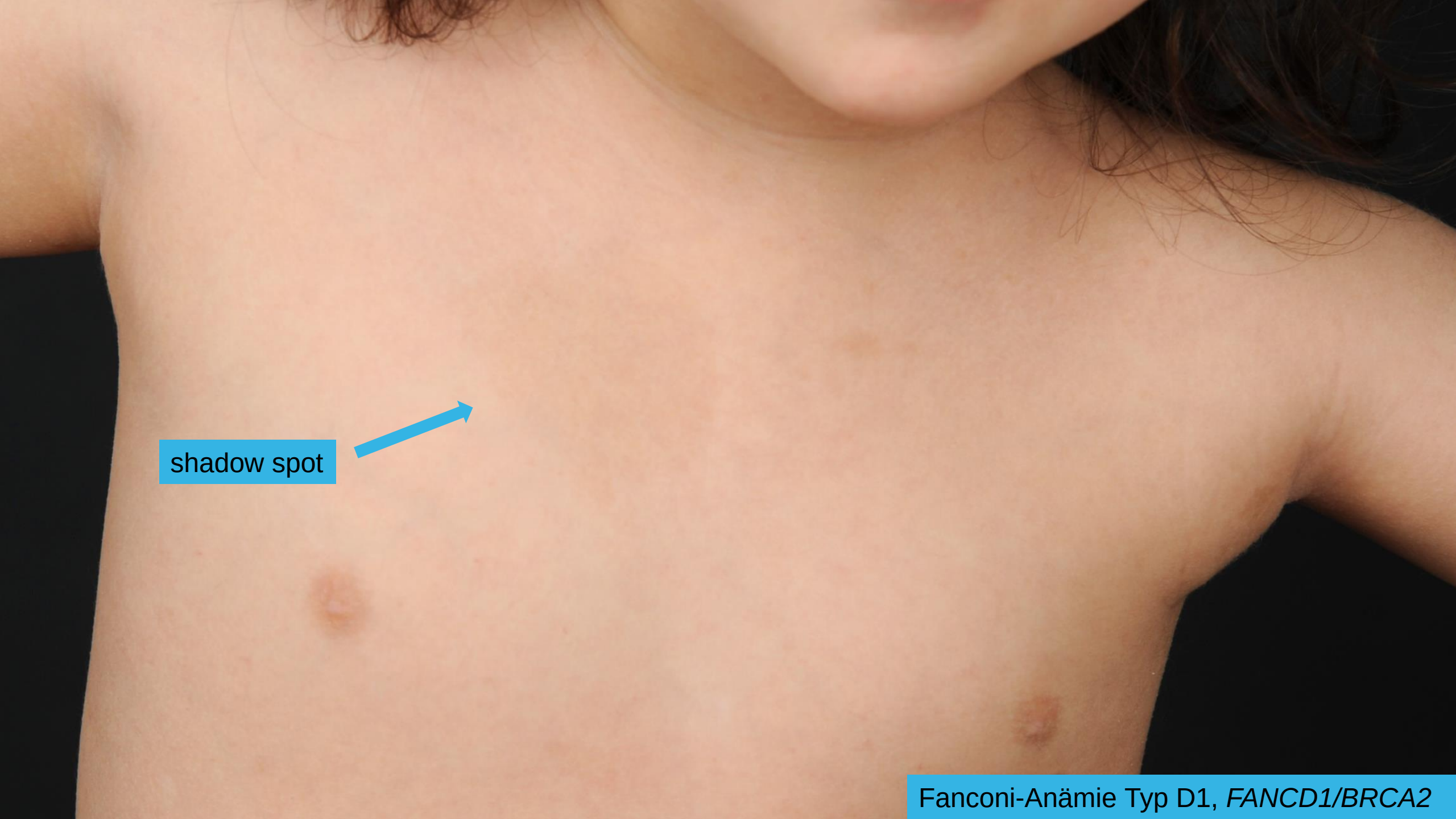
Weisse, rote oder blaue Flecken

Konsanguinität

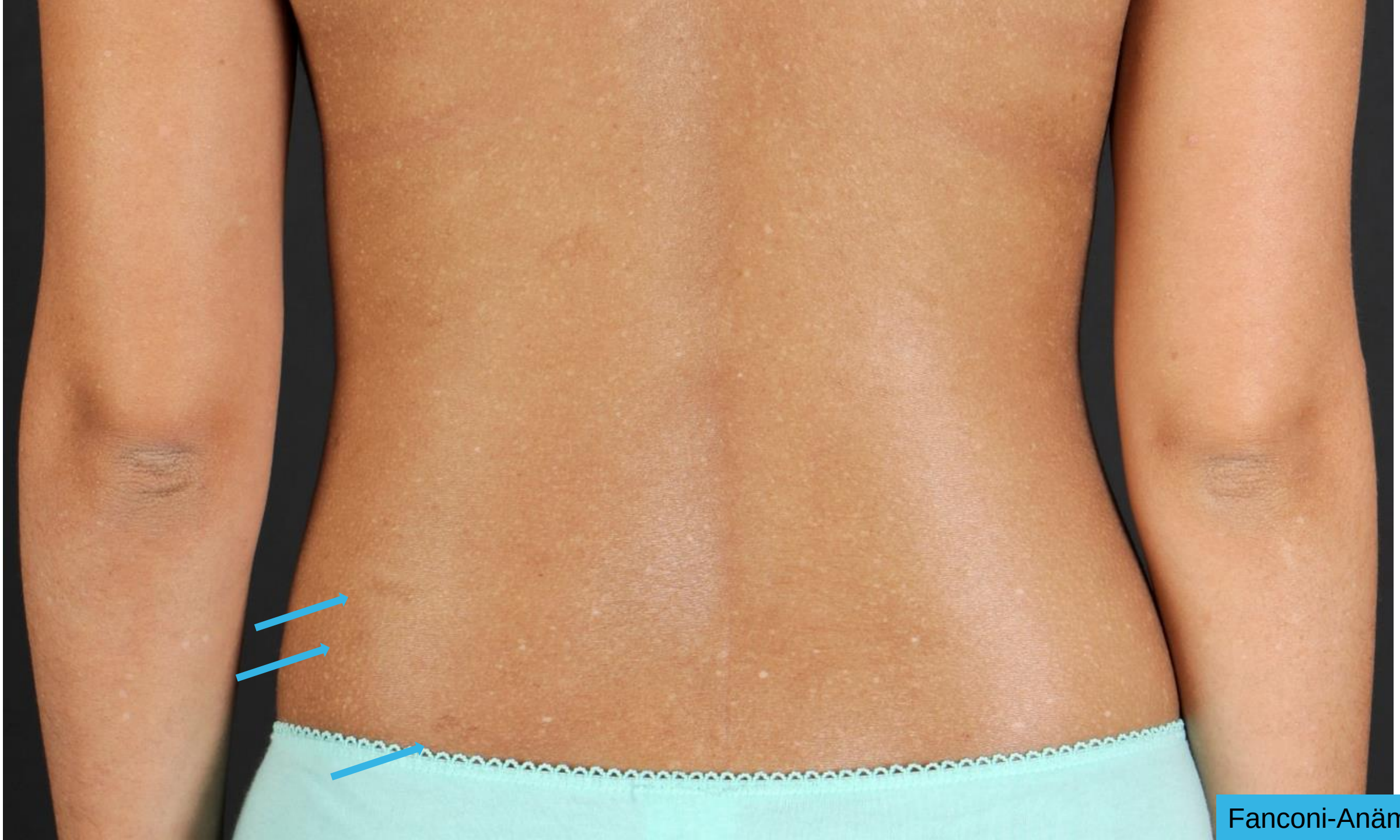
Tumoren in PA oder FA

- ZNS
- GIT, gynäkologisch
- hämatologisch

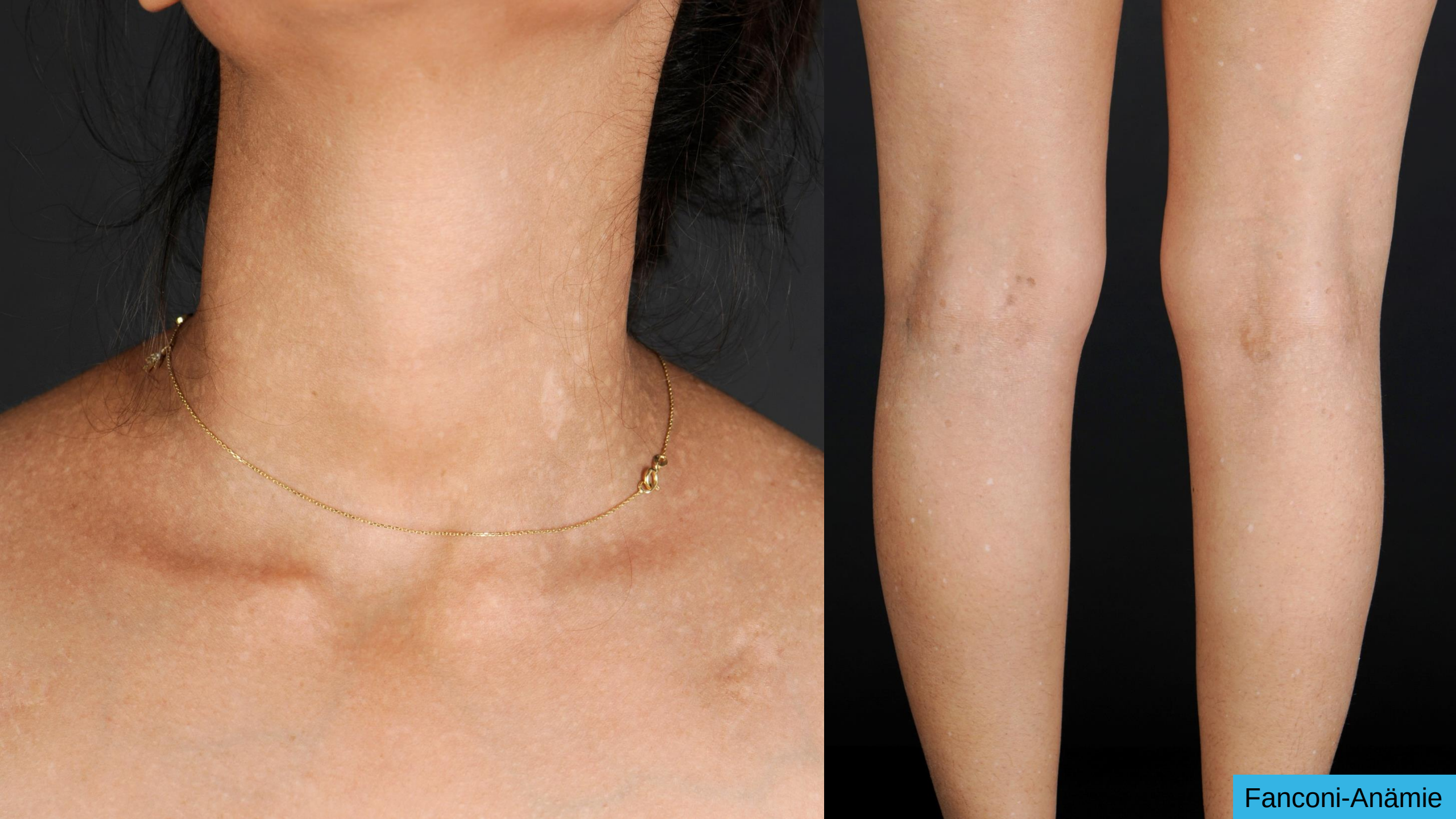




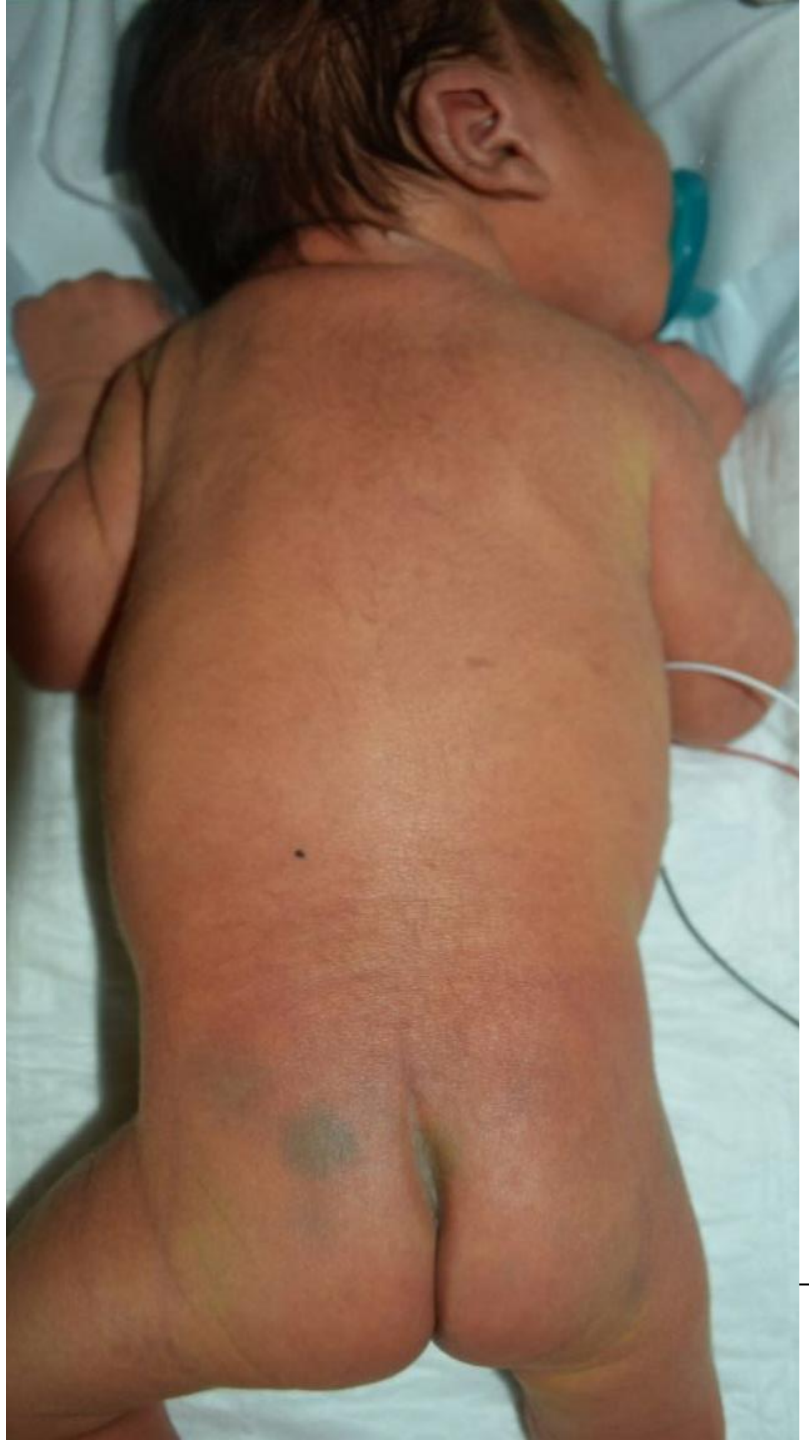
Fanconi-Anämie Typ D1, *FANCD1/BRCA2*

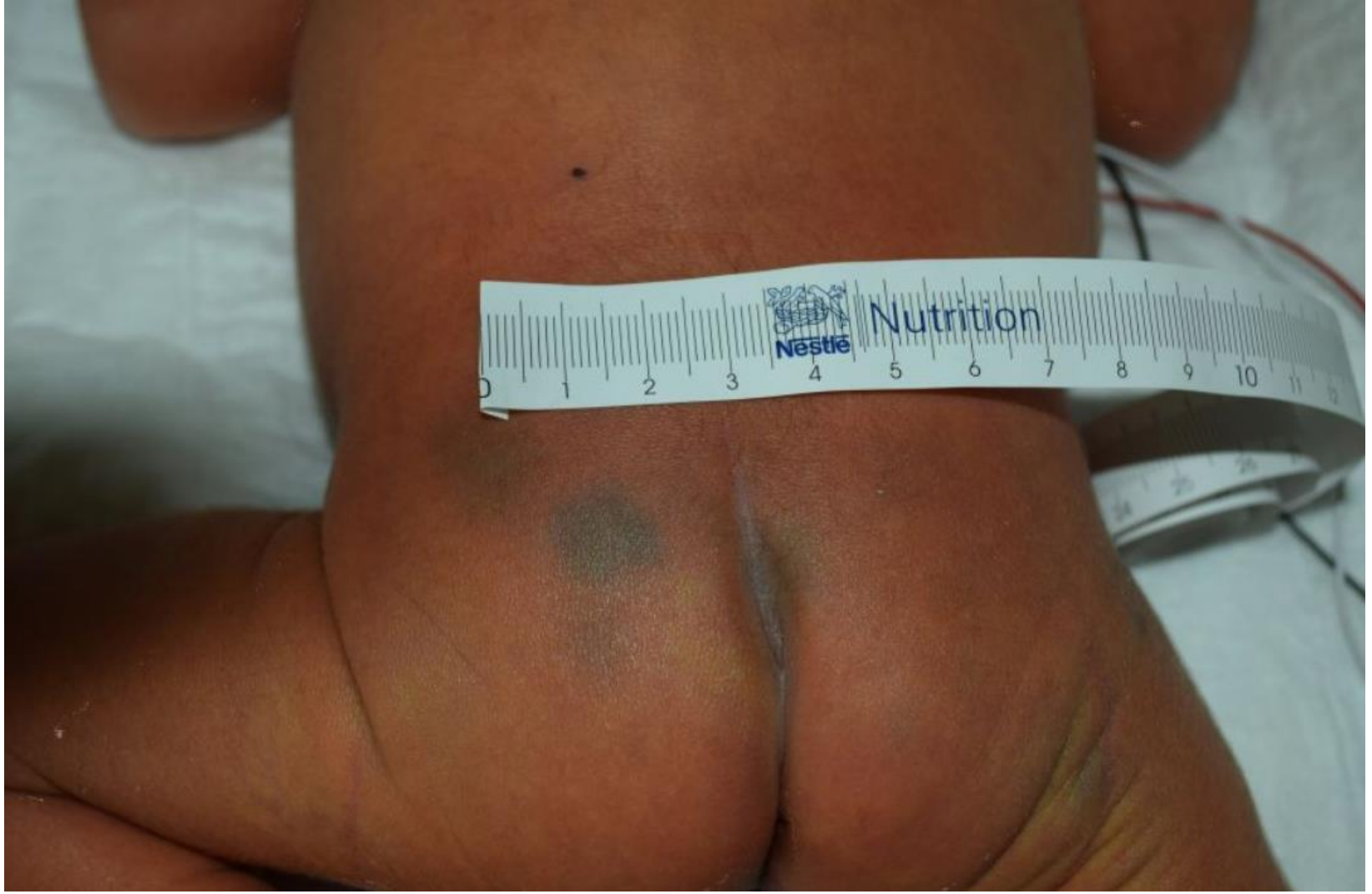


Fanconi-Anämie



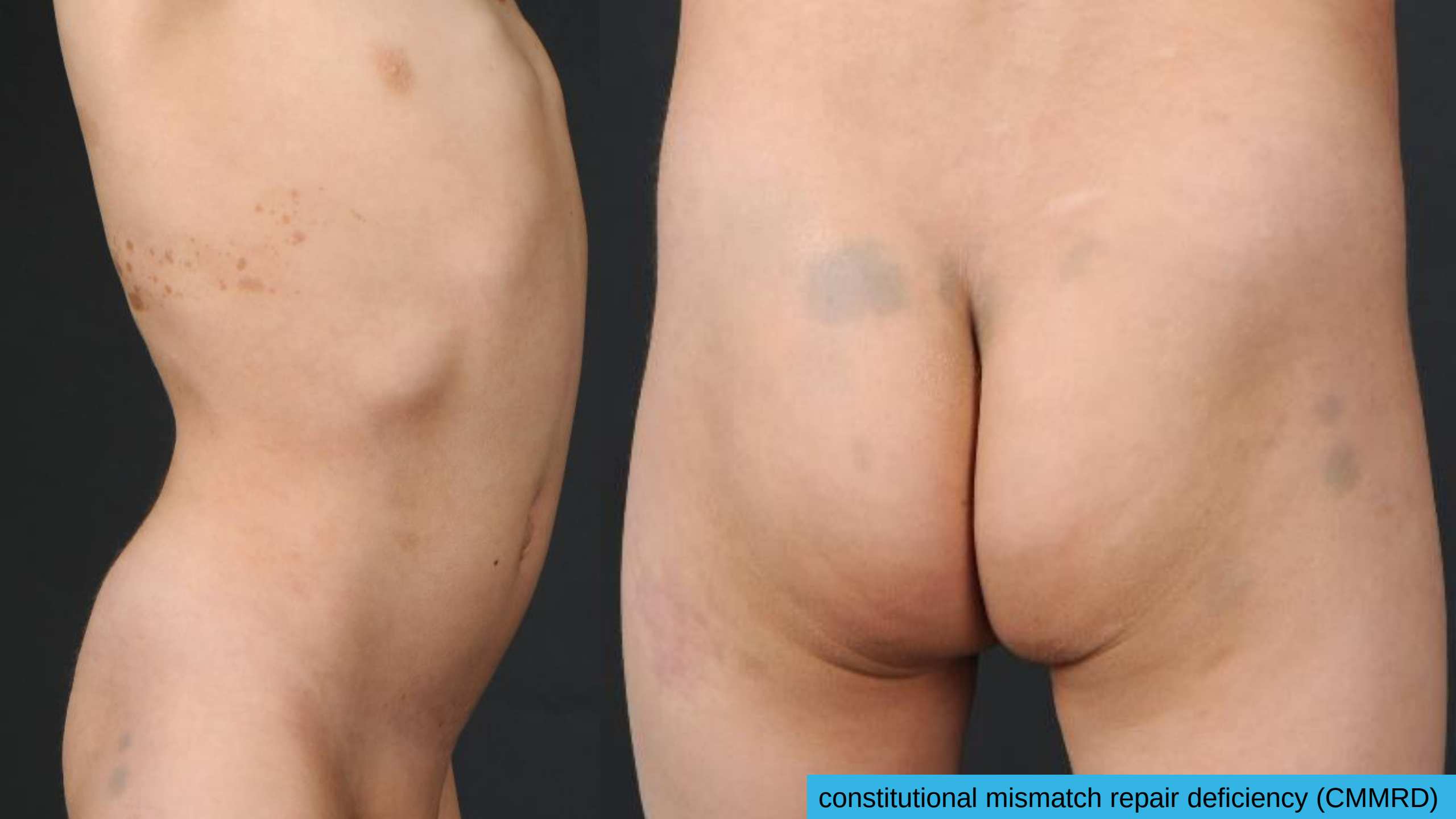
Fanconi-Anämie





Teledermatologie-Konsil (A. Schwieger-Briel)

- termingeborener Knabe
- tumorösen Raumforderung im linken Ventrikel
- multiple braune und blaue Flecken
- KM mit Lynch-Syndrom



constitutional mismatch repair deficiency (CMMRD)

Constitutional mismatch repair deficiency (CMMRD)

- MMR-Gene (*MSH2, MSH6, MLH1, PMS2*)
- **Heterozygote Träger → Lynch-Syndrom** (vgl. Muir-Torre Syndrom)
  - Gastrointestinale und urogenitale Tumoren im Erwachsenenalter
- **Homo- oder Compound-heterozygote Träger → CMMRD**
  - Multiple, aggressive Tumoren im Kindesalter
  - Viele erreichen Erwachsenenalter nicht

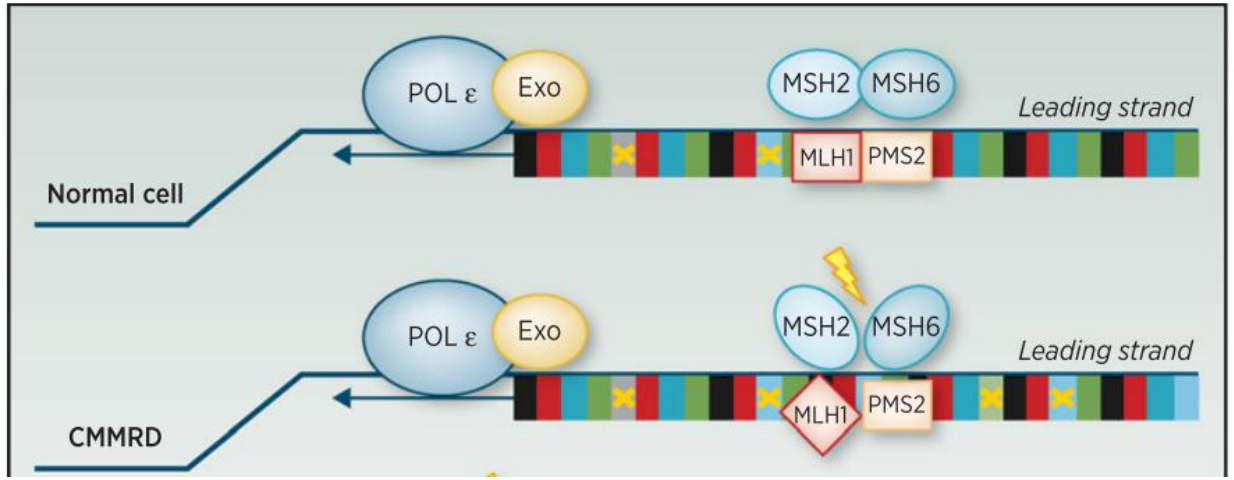


Table 2. Surveillance protocol for patients with CMMRD

Examination	Start age	Frequency	Tumors
MRI brain	At diagnosis	Q 6 months	Brain tumors
WBMRI	6 years	Once a year	All tumors
CBC	1 year	Q 6 months	Leukemia
Abdominal U/S	1 year	Q 6 months	Lymphoma
Upper gastrointestinal endoscopy; VCE, ileocolonoscopy	4 to 6 years	Once a year	Gastrointestina tumors
GYN exam, transvaginal U/S, pipelle curettage, urine cytology, dipstick	20 years	Once a year	Genitourinary cancers

Abbreviations: GYN, gynecologic; Q, every; U/S, ultrasound; VCE, visual capsule endoscopy.

Clin Cancer Res; 23(11) June 1, 2017

Clin Genet 2017: 91: 507–519
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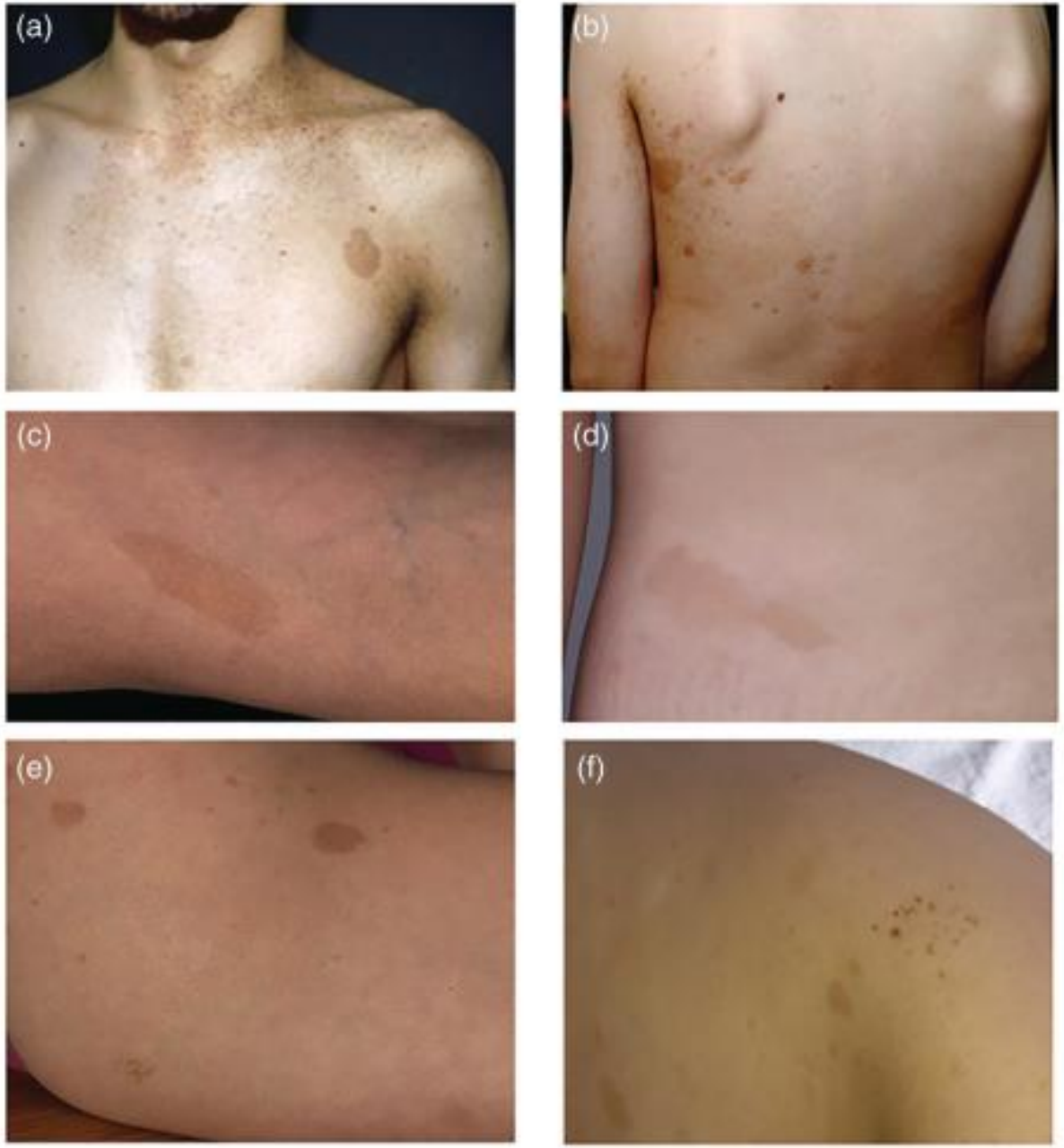
CLINICAL GENETICS
doi: 10.1111/cge.12904

Review

Connections between constitutional mismatch repair deficiency syndrome and neurofibromatosis type 1

Wimmer K., Rosenbaum T., Messiaen L. Connections between constitutional mismatch repair deficiency syndrome and neurofibromatosis type 1. Clin Genet 2017: 91: 507–519. © John Wiley & Sons A/S. Published by

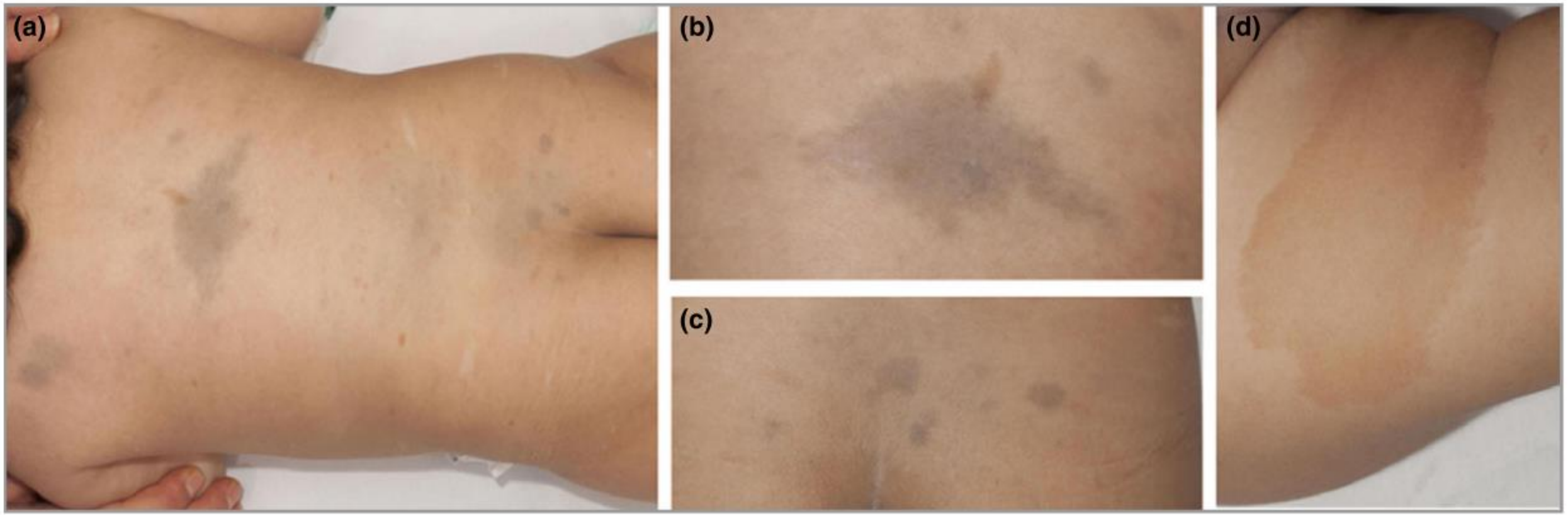
K. Wimmer[a], T. Rosenbaum[b] and L. Messiaen[c]



NF1

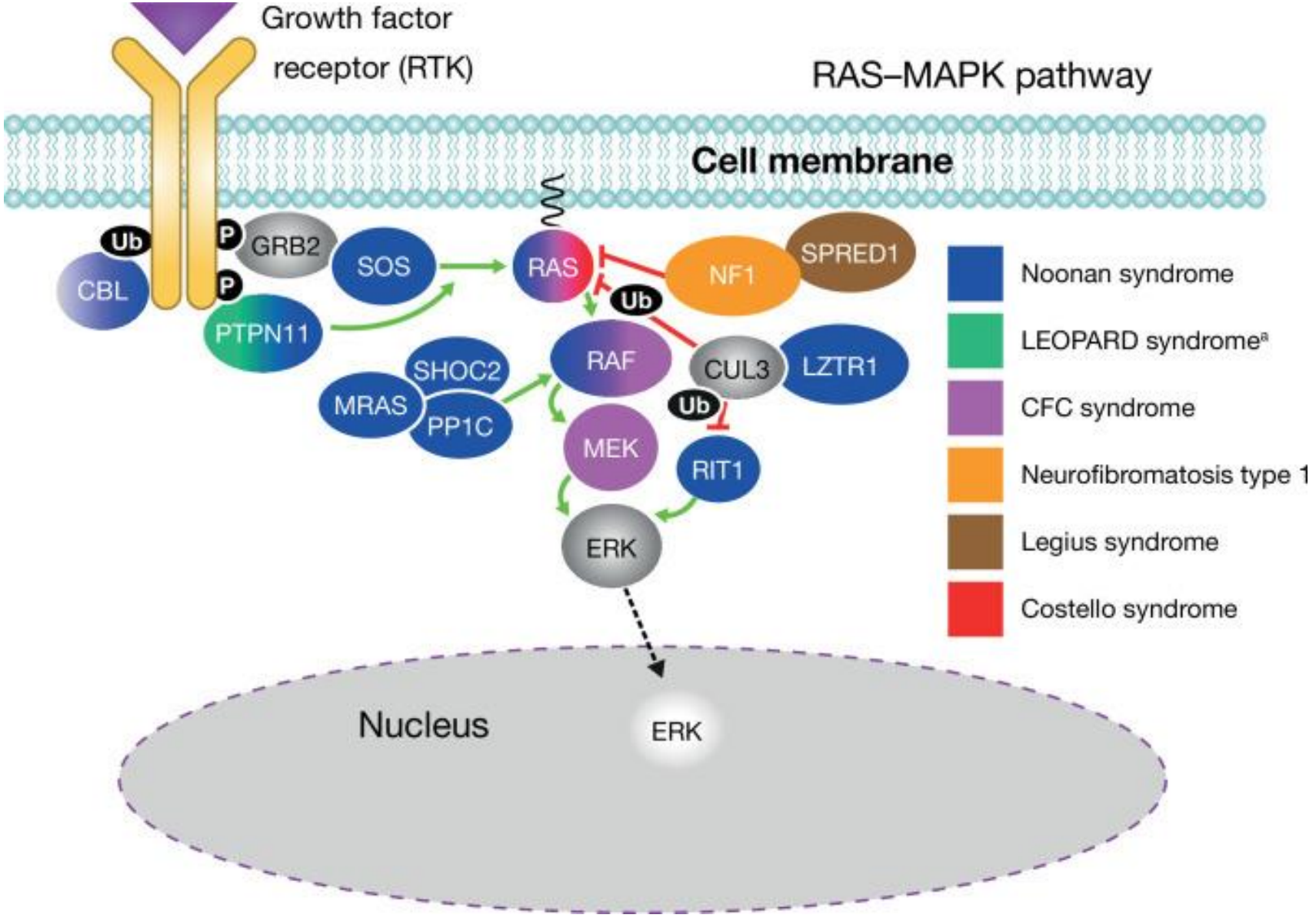
CMMRD

Atypical dermal melanocytosis: a diagnostic clue in constitutional mismatch repair deficiency syndrome

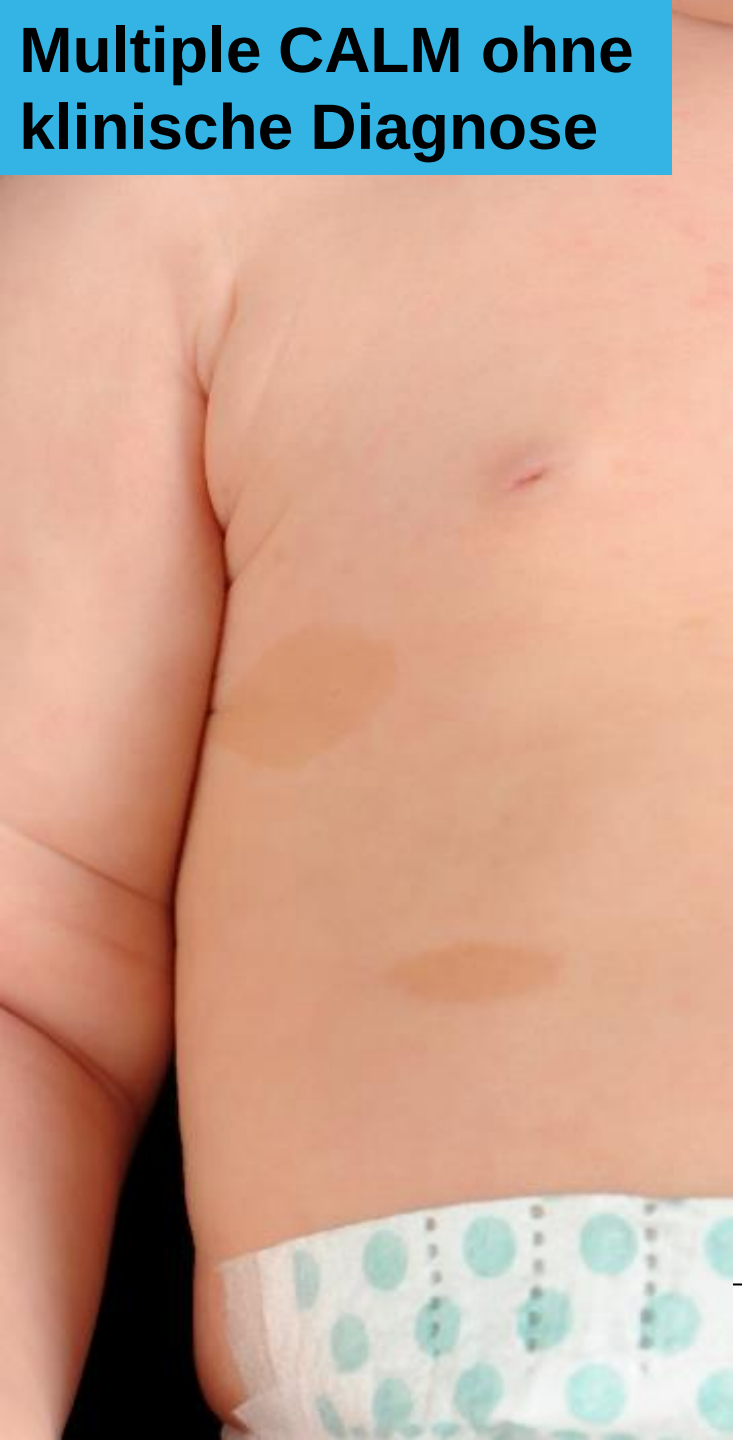


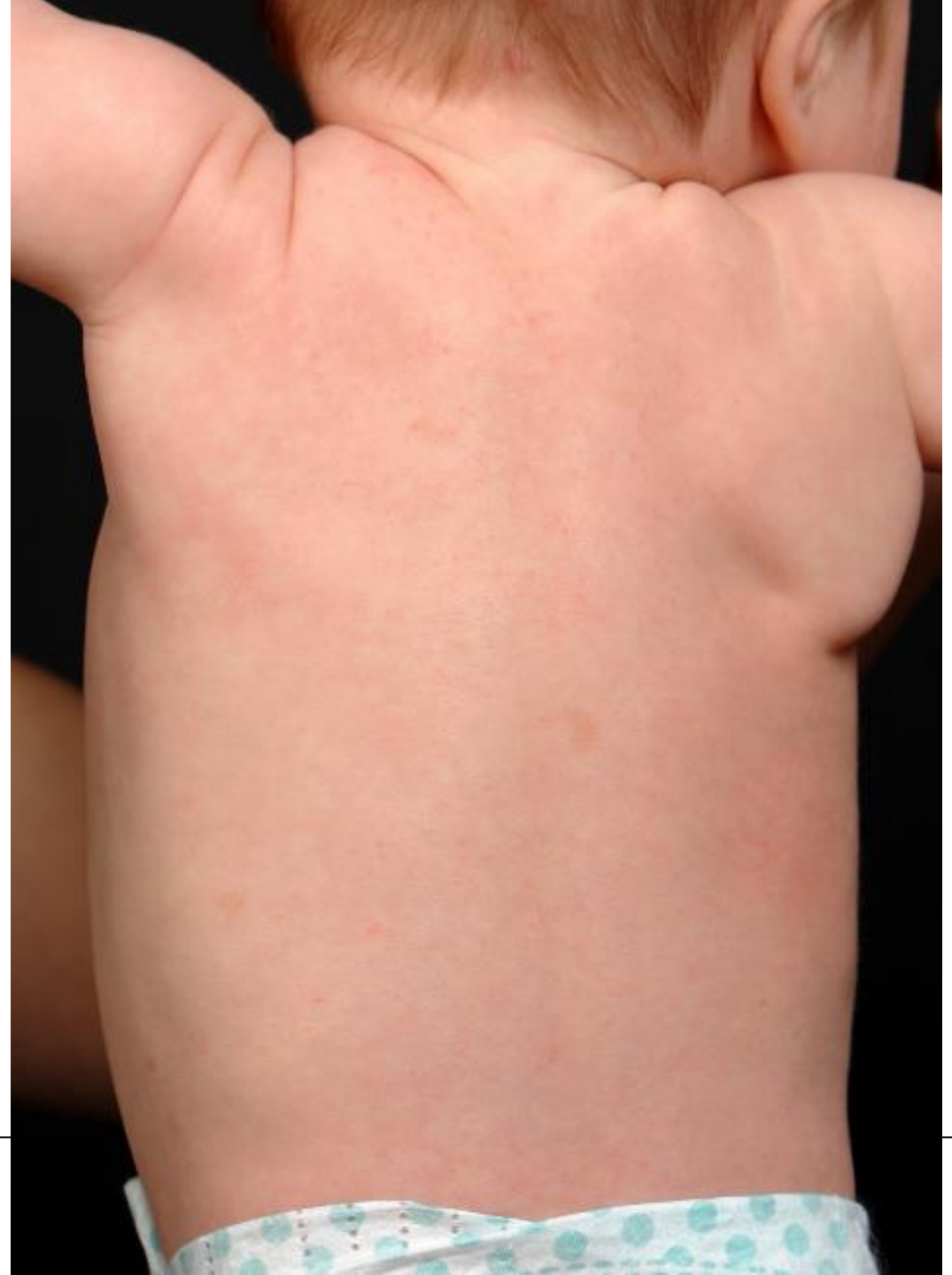
Polubothu et al, Br J Dermatol, 2017

RASopathien



Multiple CALM ohne klinische Diagnose



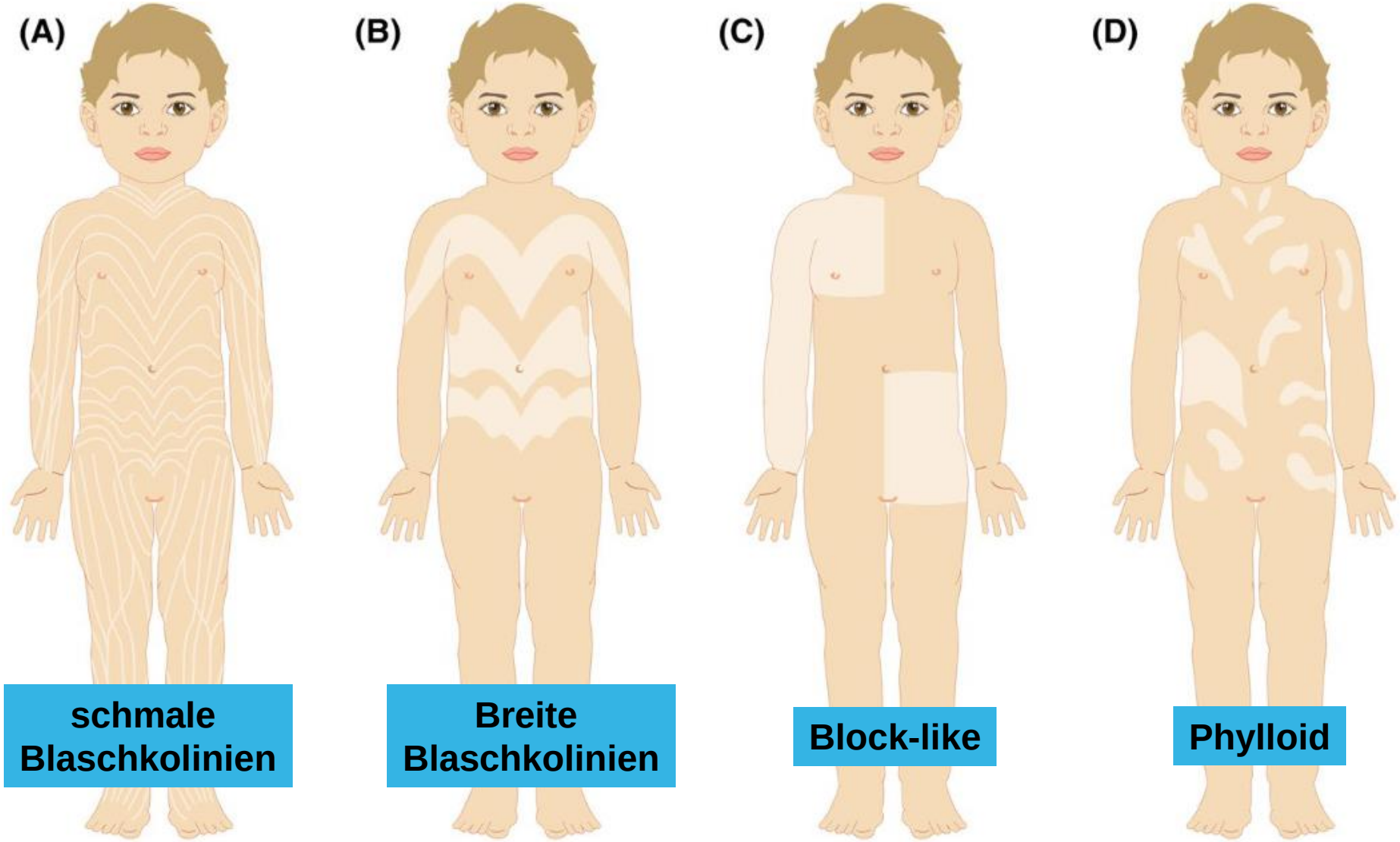


Molekulargenetische Untersuchung

NF1 + Legius

andere RASopathien, CMMRD, Fanconi

Pigmentmosaike



schmale Blaschkolinien

Breite Blaschkolinien

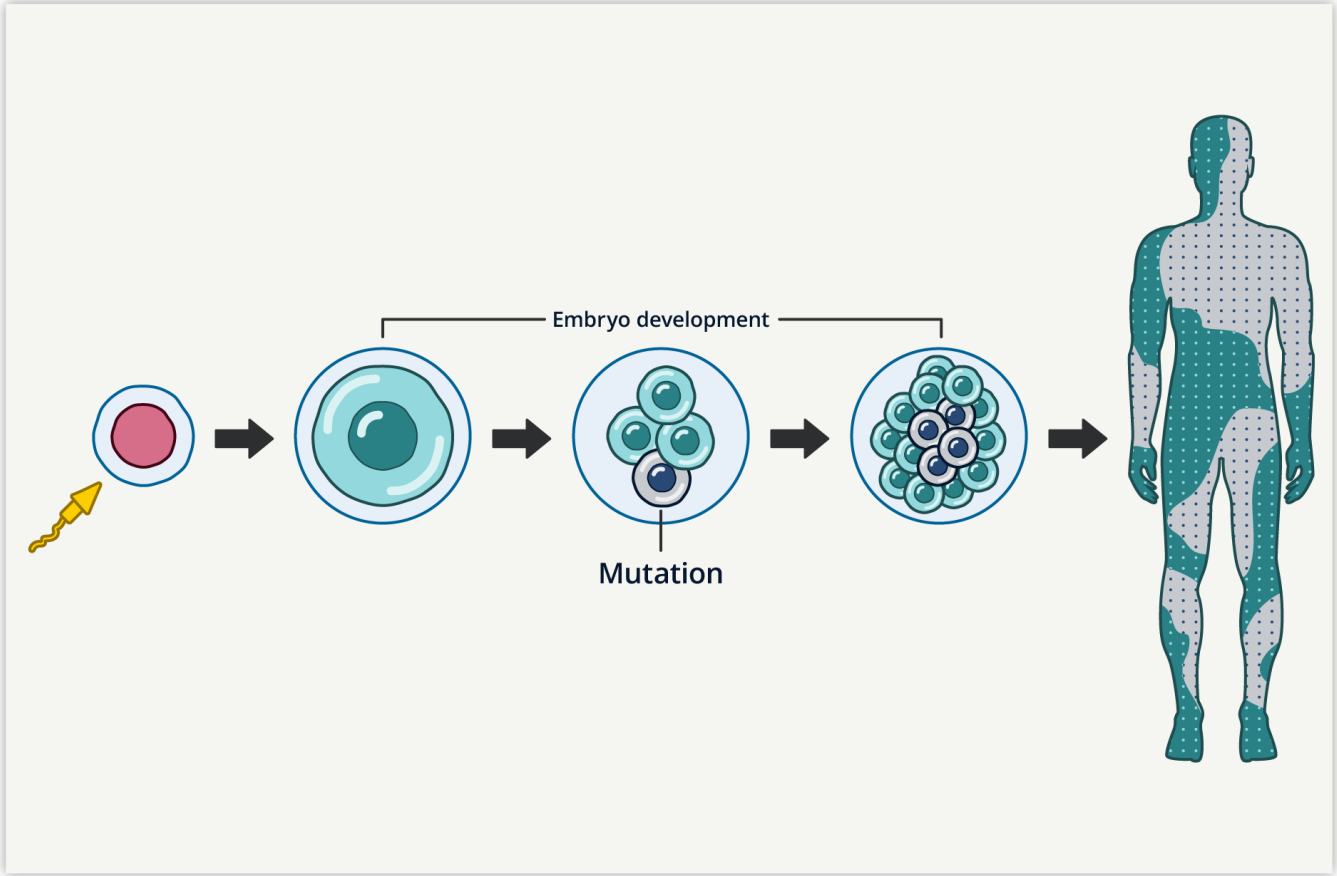
Block-like

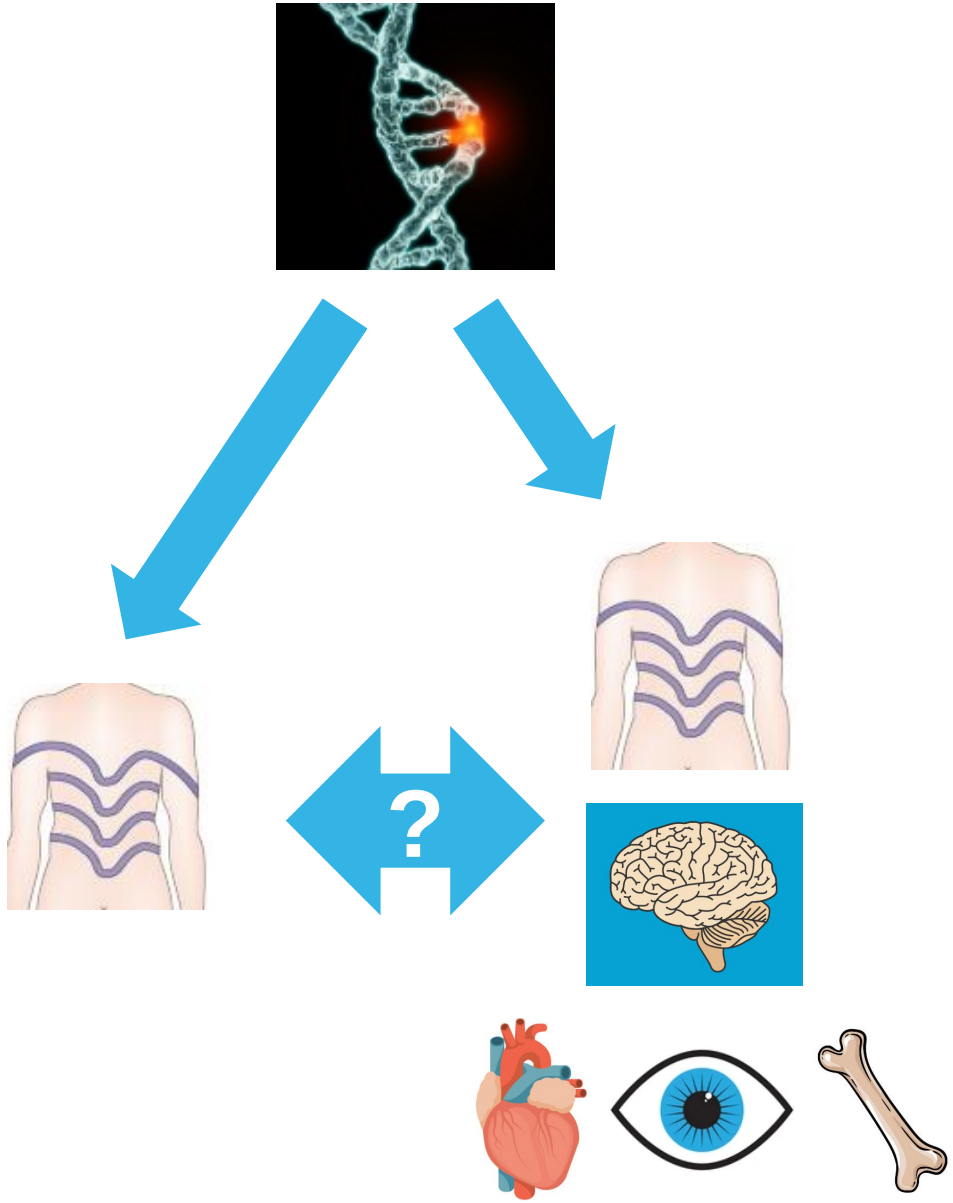
Phylloid

BRAUN oder WEISS

Belzile E et al, Pediatr Dermatol 2019
Schaffer JV, Clin Dermatol 2022

Mosaikerkrankungen der Haut





«nevoid hypo-/hypermelanosis»

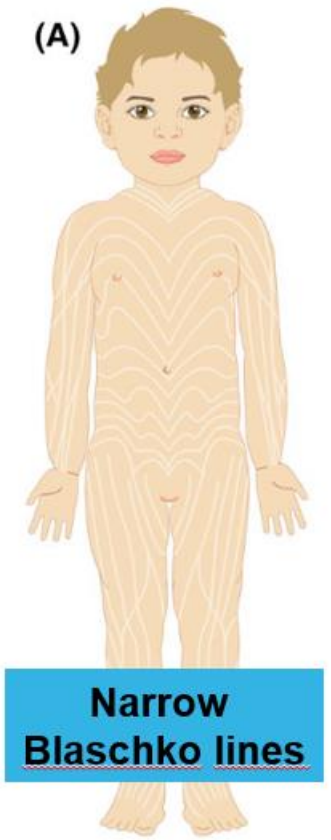
«patterned pigmentation»

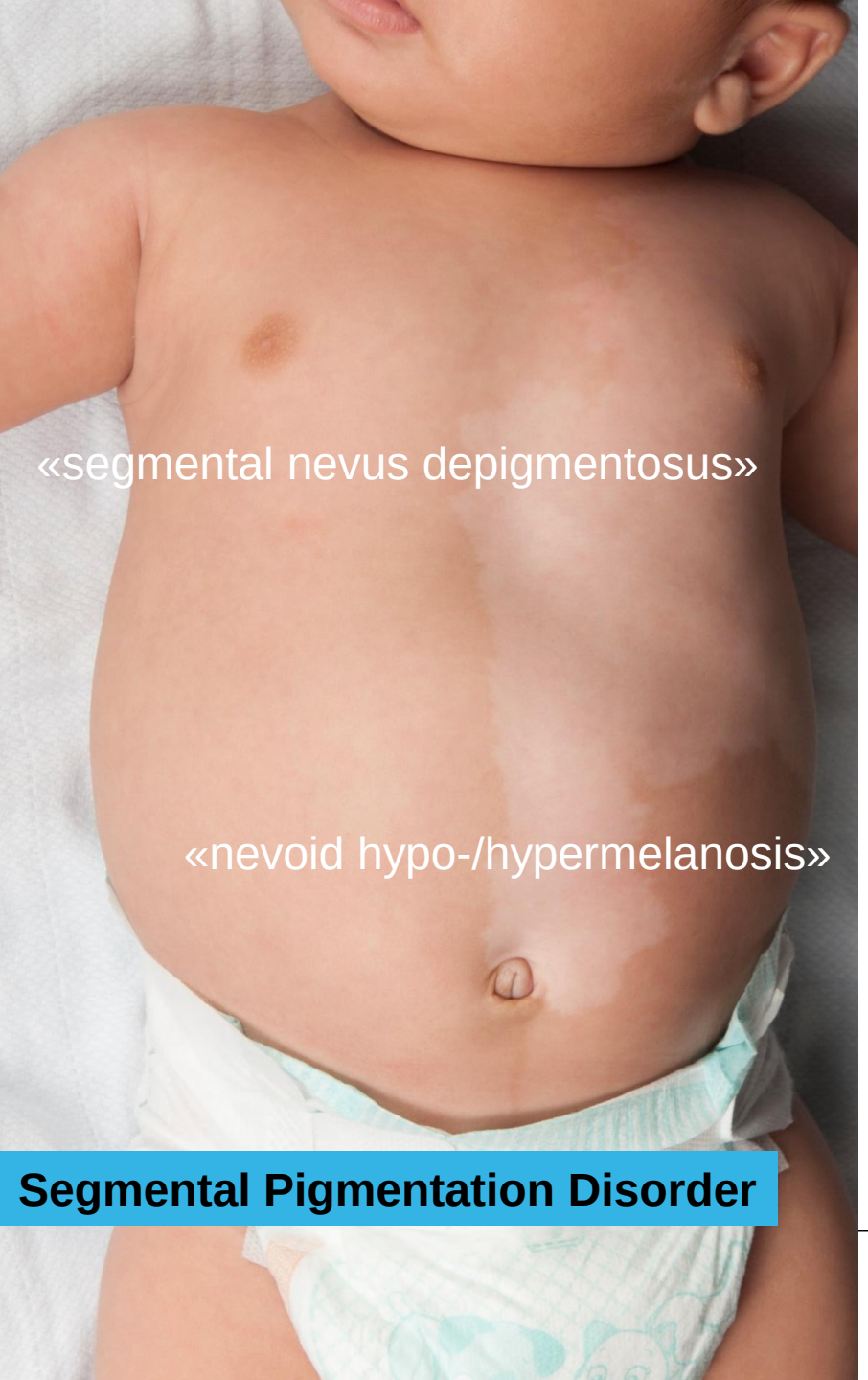
«Hypomelanosis of Ito»

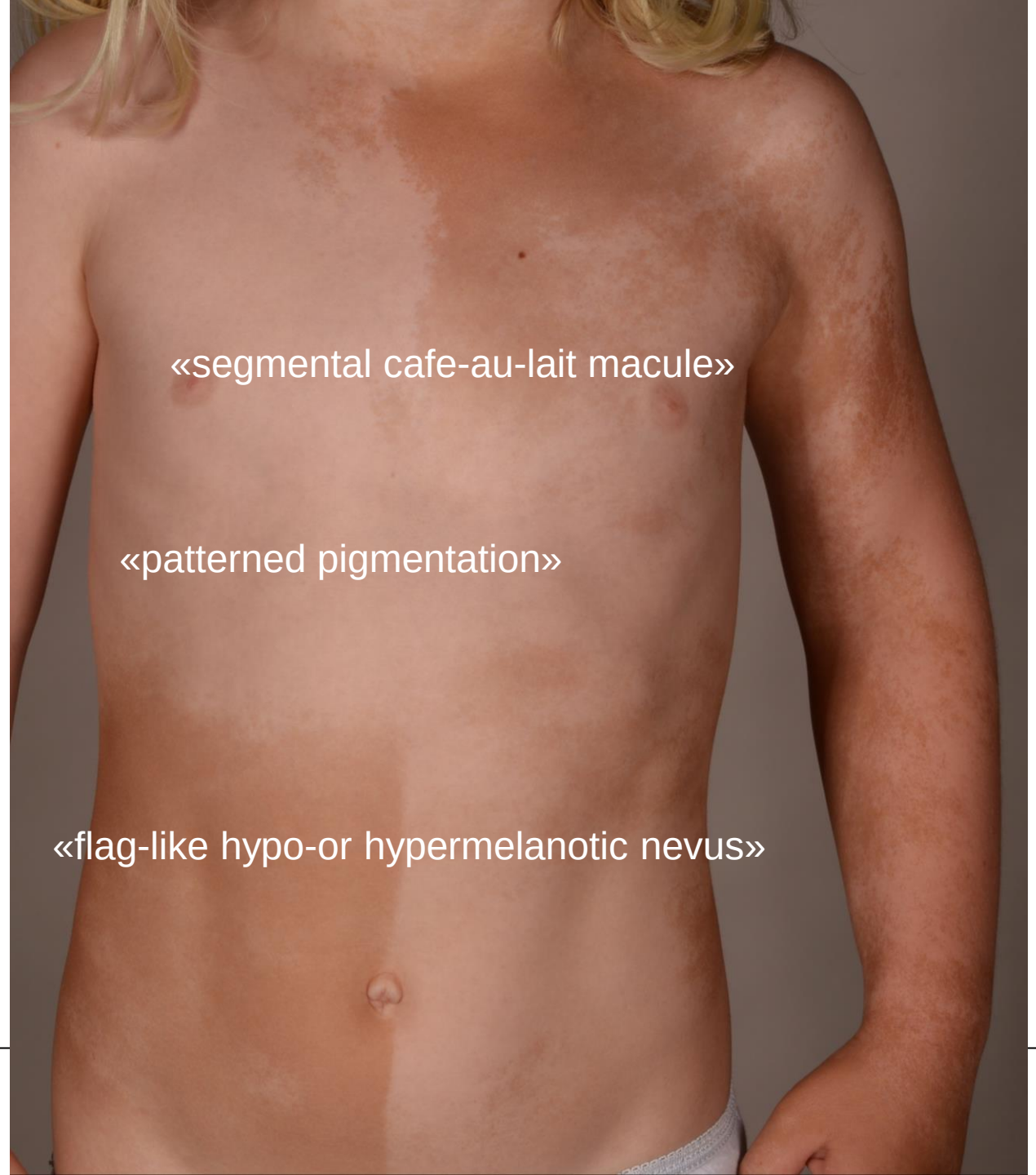
«linear and whorled nevoid hypermelanosis»

«Blaschkoid dyspigmentation»

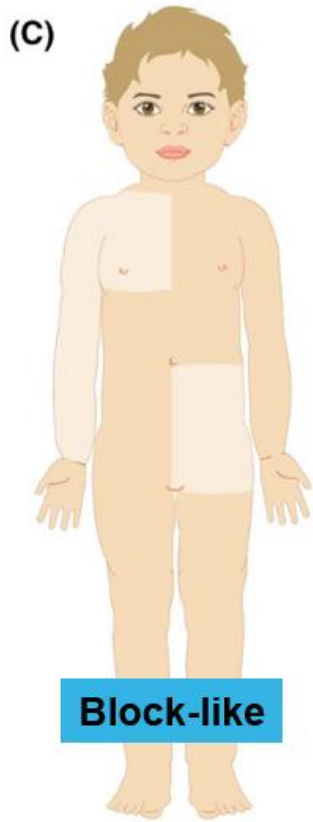
Lineäre nävoide Hypo- (or Hyper-)pigmentation

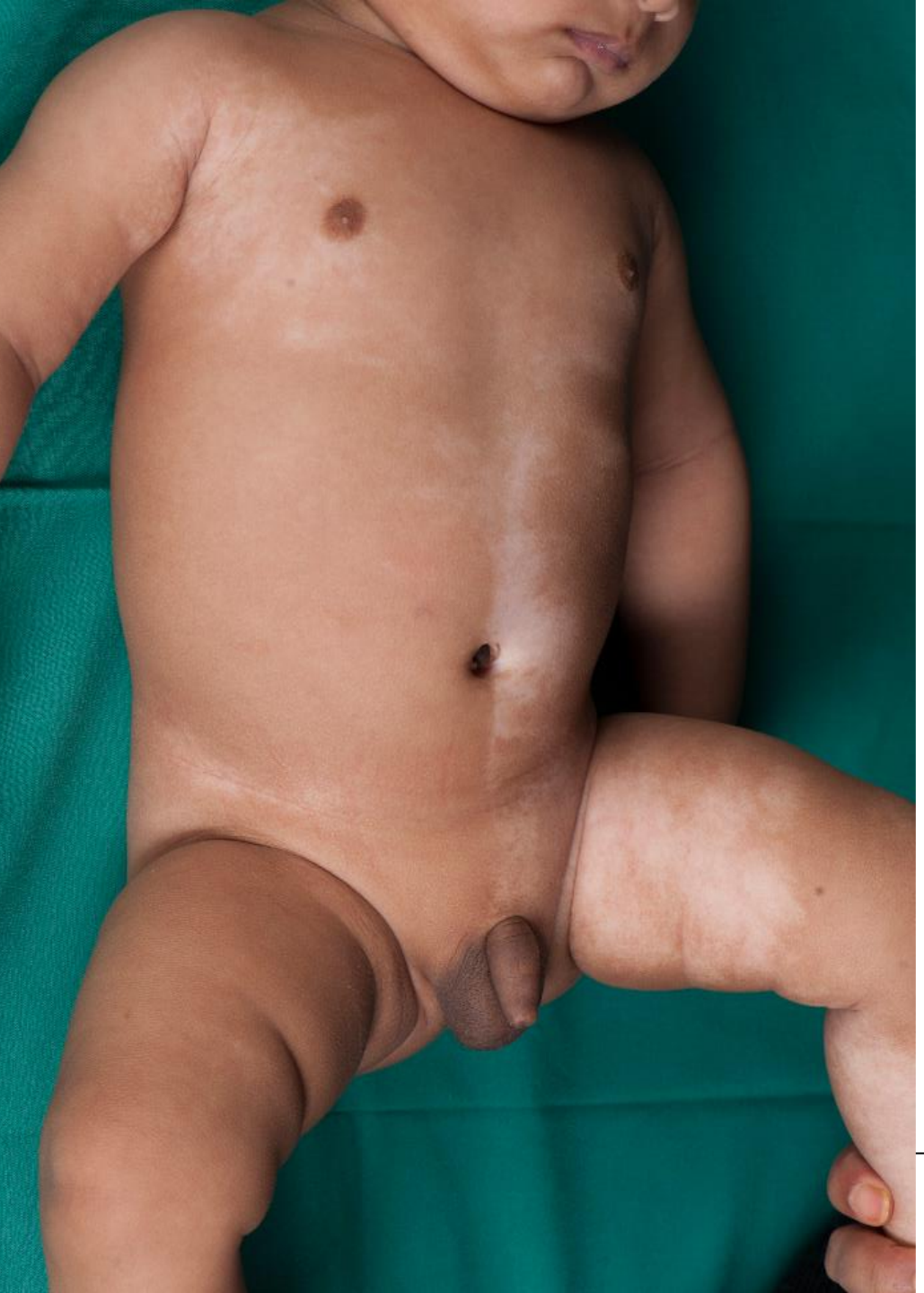






Segmental Pigmentation Disorder





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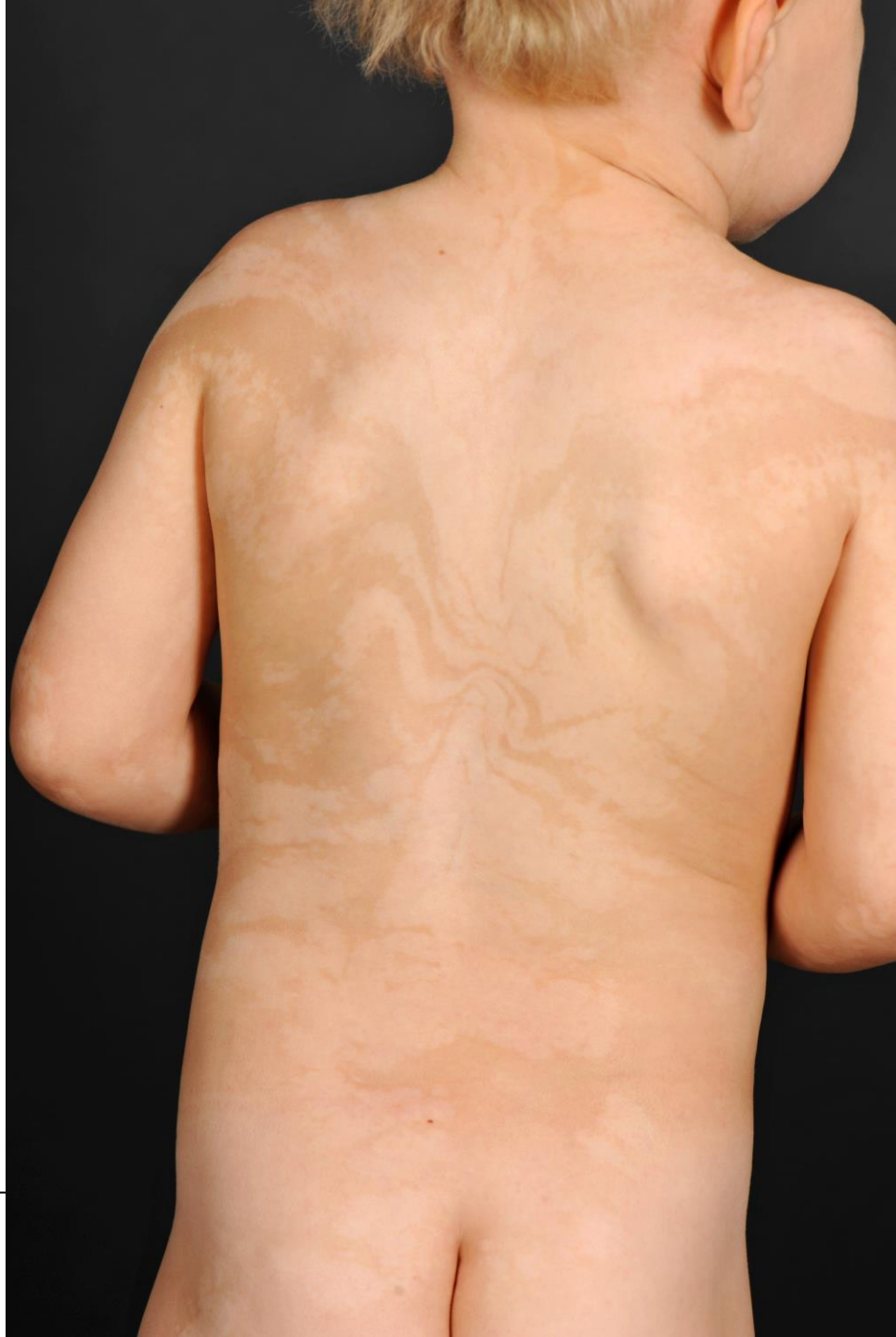


BRAUN oder WEISS – egal??

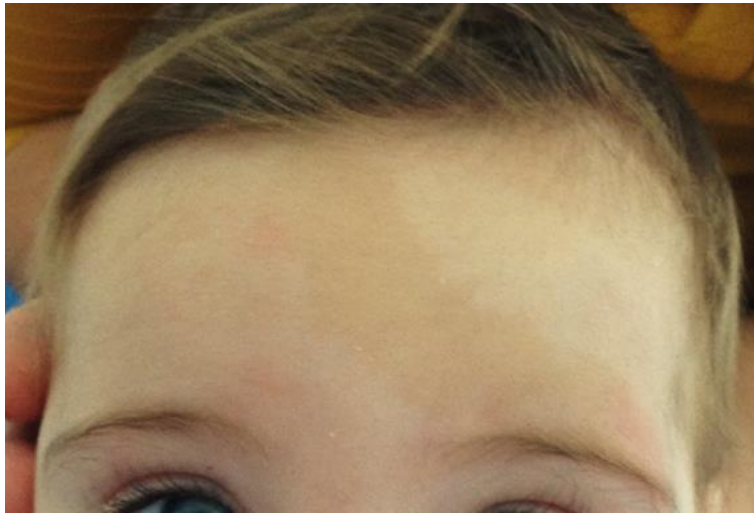
Klinischer Approach identisch

Lineäre nävoide Hypopigmentierung
grösstes Risiko für extrakutane Assoziationen(?)

Kromann Orphanet J Rare Dis, 2018
Schaffer JV, Clin Dermatol 2022

Pigmentmosaike sind keine homogene Erkrankung

- Chromosomale Aberrationen
  - 2, 3, 4, 5, 7, 8, 9, 10, 12, 13, 14, 15, 16, 18, 20, 22
  - X,Y
- Monogenetische Ursachen
  - *mTOR, RHOA, KITLG, TFE3, KNCQ5, GTF3C5*…
  - x-chromosomal: *USP9X, PHF6, POLA1*



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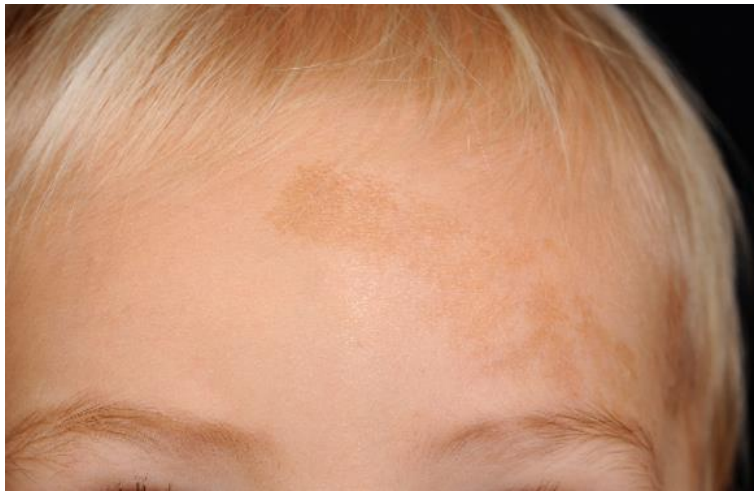
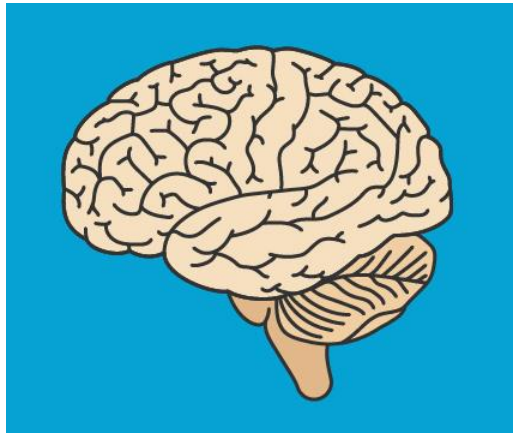


Kromann Orphanet J Rare Dis, 2018
Schaffer JV, Clin Dermatol 2022
Saida K et al, Hum Genetics 2022

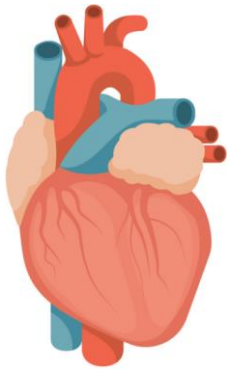
Mögliche extrakutane Assoziationen bei Pigmentmosaiken



- **am häufigsten**
- Entwicklungs-verzögerung
- Krampfanfälle
- Mikro-/Makrozephalie
- …

- Skoliose
- Syn-/Polydaktylie
- Kleinwuchs
- Dysmorphe Gesichtszüge
- …

- Kongenitale Katarakt
- …



- VSD
- PDA
- Fallot-Tetralogie
- …

… und mehr

Kromann Orphanet J Rare Dis, 2018
Schaffer JV, Clin Dermatol 2022
Treat J, Pediatr Clin N Am 2010

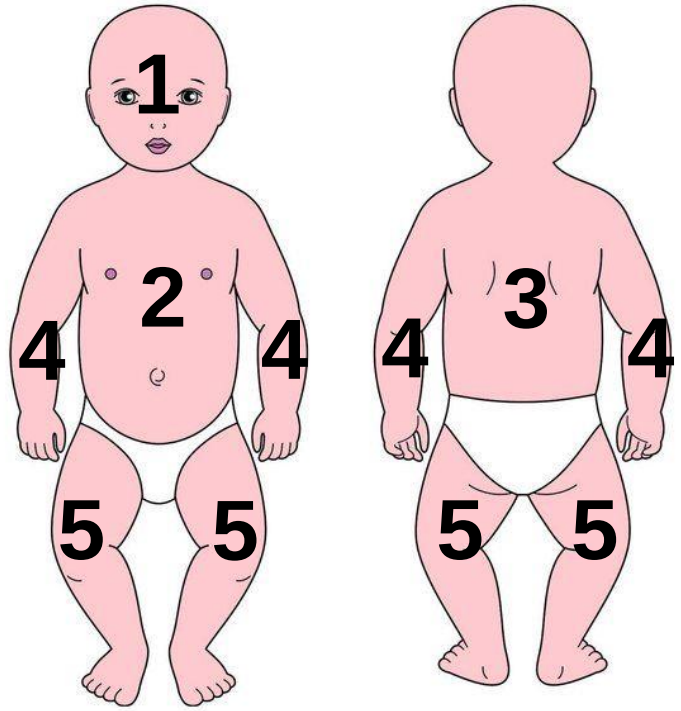
Wer hat Risiko für extrakutane Assoziationen?

- viel Ascertainment- und Reporting-Bias in der Literatur
- für alle Typen zusammengenommen **< 10%**
- Segmental Pigmentation Disorder **sehr kleines Risiko**
- Lineäre nävoide Hyper-/Hypopigmentation
  - **abhängig vom Ausmass des Hautbefalls**
  - **weiss möglicherweise > braun**

Kromann Orphanet J Rare Dis, 2018
Schaffer JV, Clin Dermatol 2022
Oren-Shabtai M et al, Acta Derm Ven 2022

Patterned cutaneous hypopigmentation phenotype characterization: A retrospective study in 106 children

Eugénie Belzile MD[1] | Catherine McCuaig MD[1] | Jean-Baptiste Le Meur PhD[2] | Jérôme Coulombe MD[1] | Afshin Hatami MD[1] | Julie Powell MD[1] | Jean-Baptiste Rivière PhD[3,4] | Danielle Marcoux MD[1]



- 5 body regions
  - face, anterior trunk, posterior trunk, upper and lower extremities

- **Neurologic and developmental**
  - **4 or 5 regions involved: 33 and 40%**
  - **1 to 3 regions involved: 8 and 11%**

- any extracutaneous finding
  - 4 or 5 regions involved: 40 – 60%
  - 1 to 3 regions involved: 17 – 28%

Vorgehen bei Pigmentmosaiken

Anamnese und klinische Untersuchung

extrakutane Manifestationen

ja

Zuweisung SpezialistIn

Genetische Untersuchung

- Blut UND Haut!

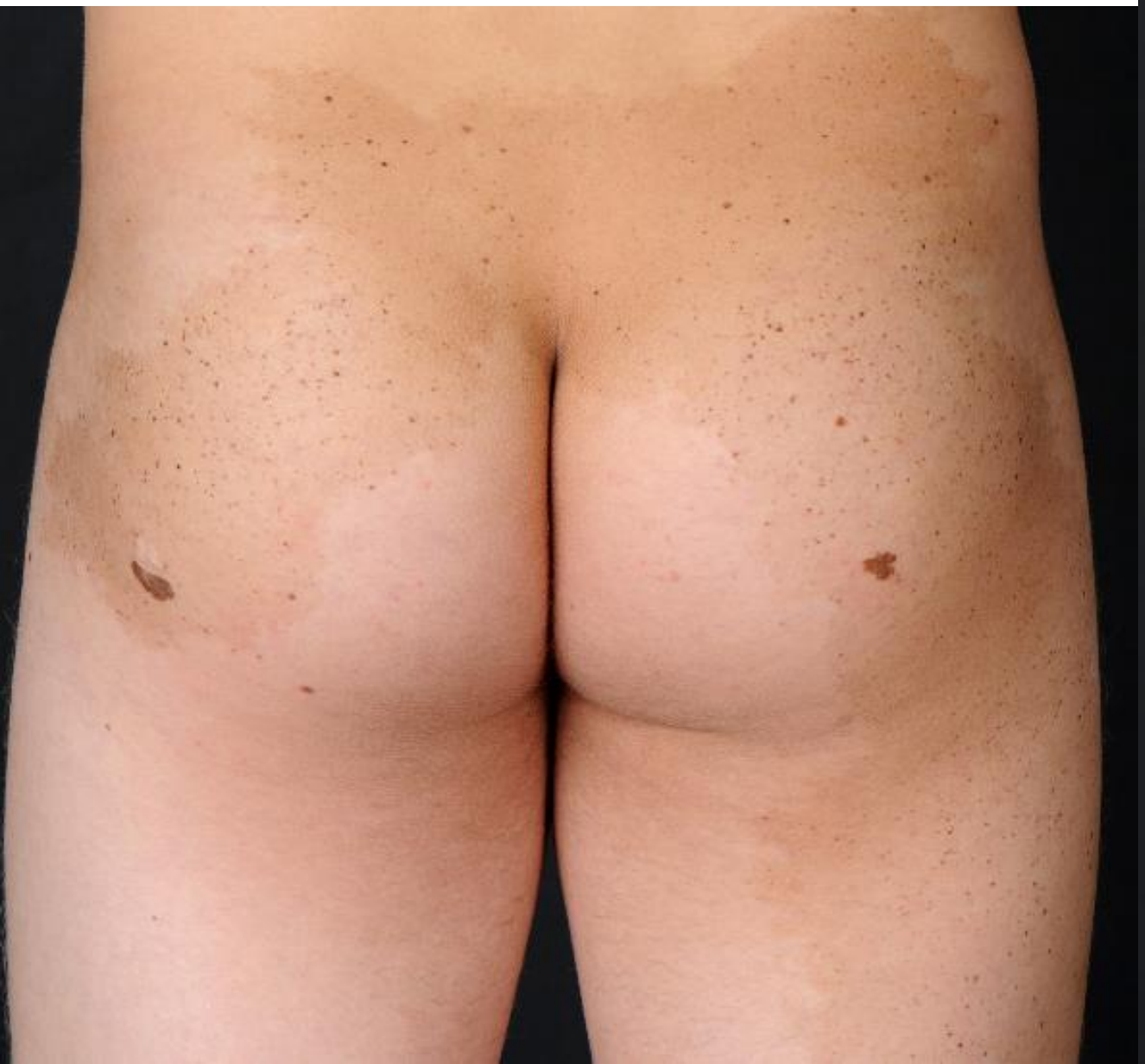
nein

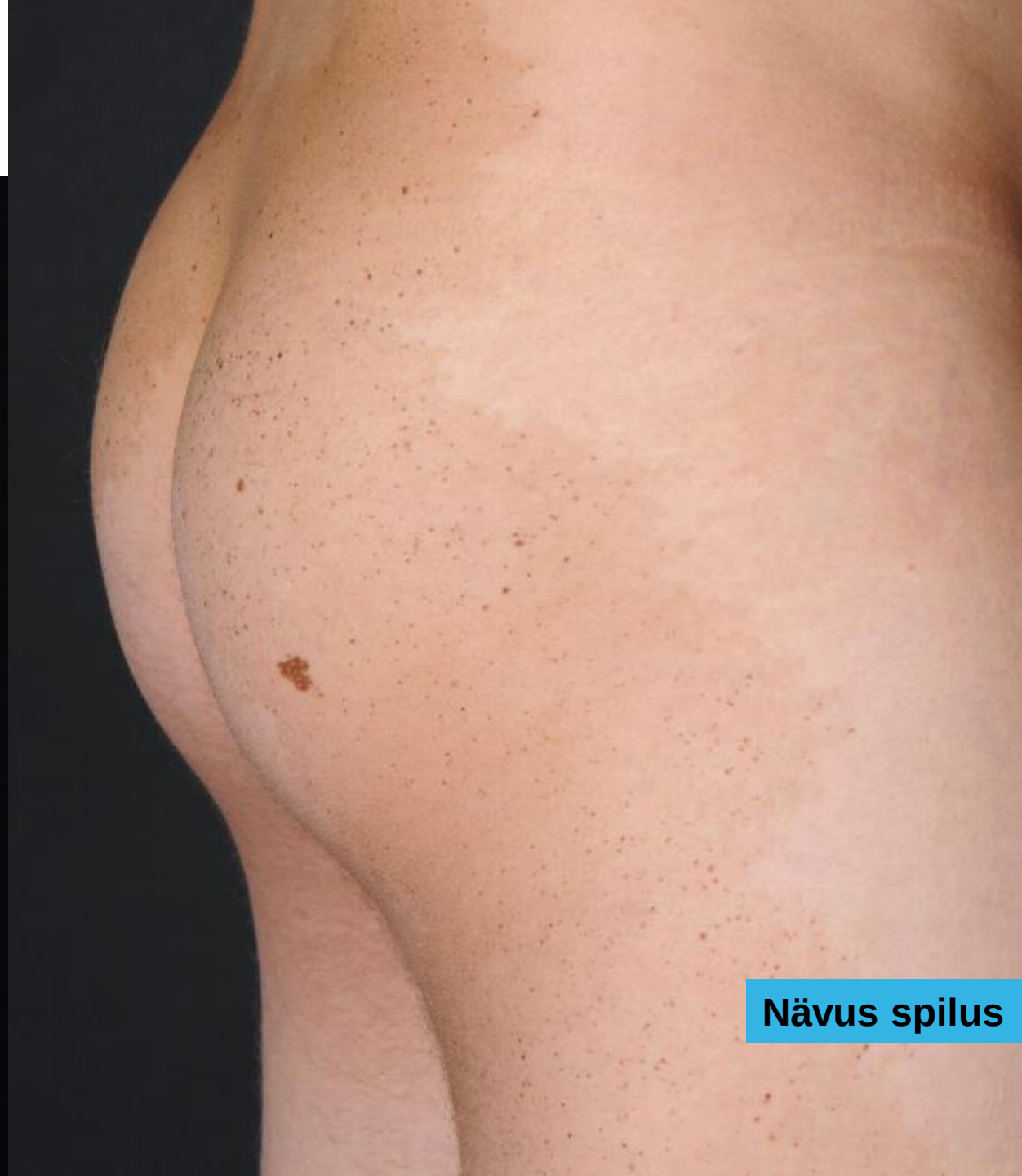
regelmässiger pädiatrischer und dermatologischer Follow-up

Differentialdiagnosen

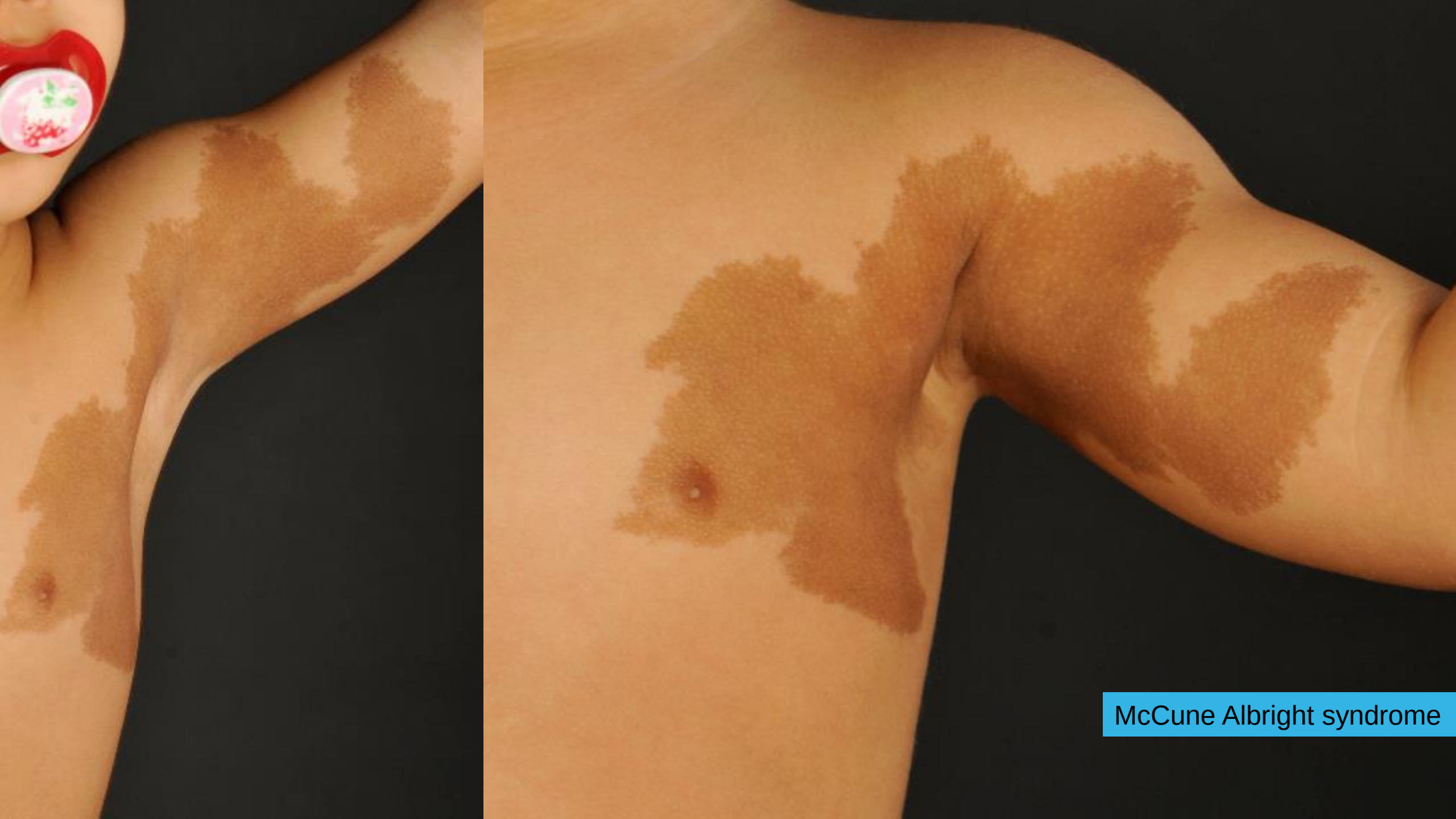
Mosaik Neurofibromatose

Differentialdiagnosen





Nävus spilus


McCune Albright syndrome

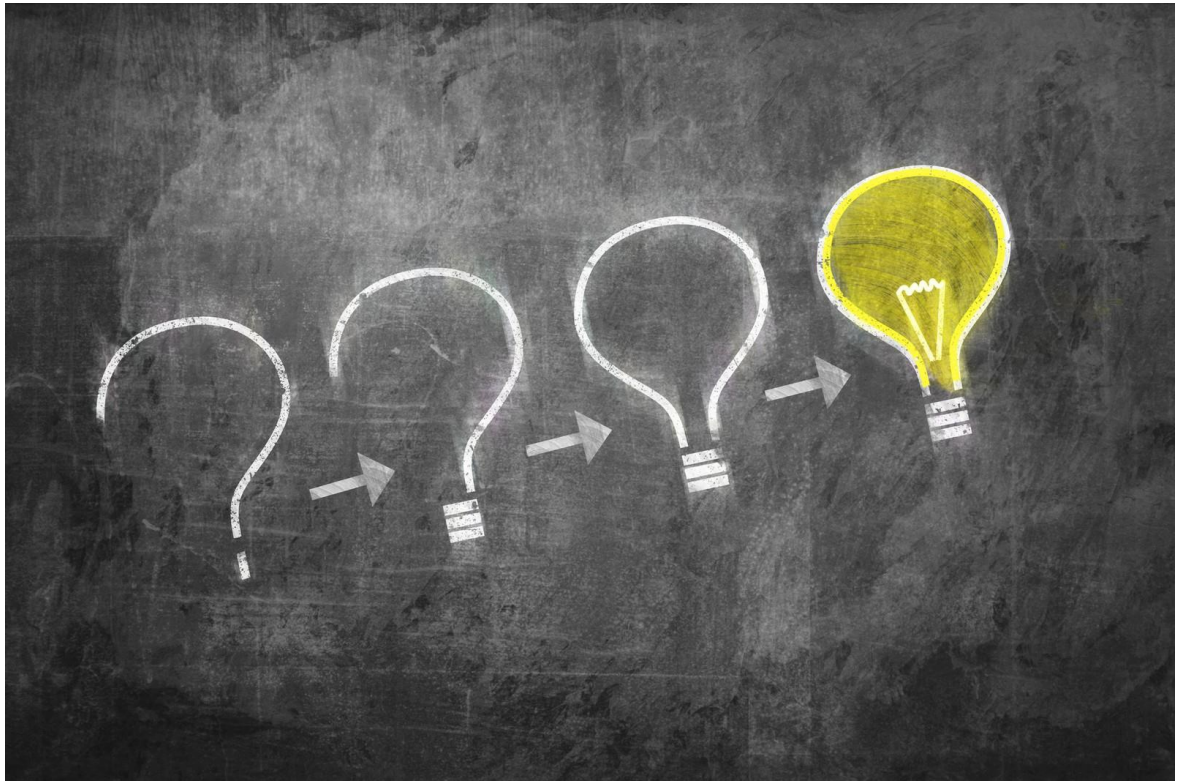
Differentialdiagnosen

Segmentale Vitiligo

Differentialdiagnosen

Lichen striatus

Vielen Dank für die Aufmerksamkeit !



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